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a scientific corner

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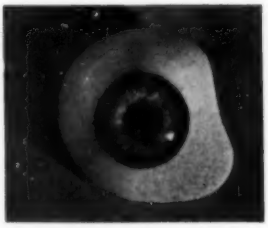

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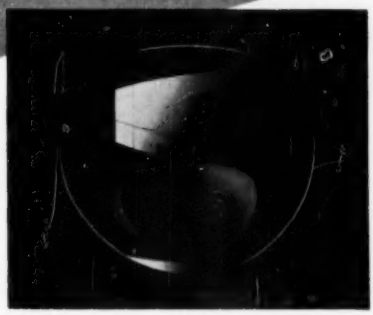

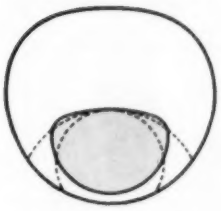

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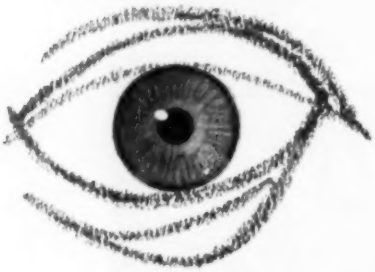

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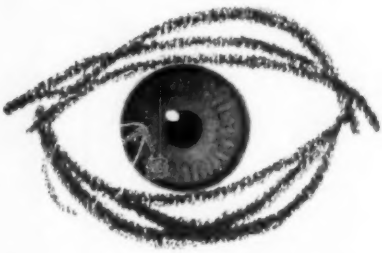

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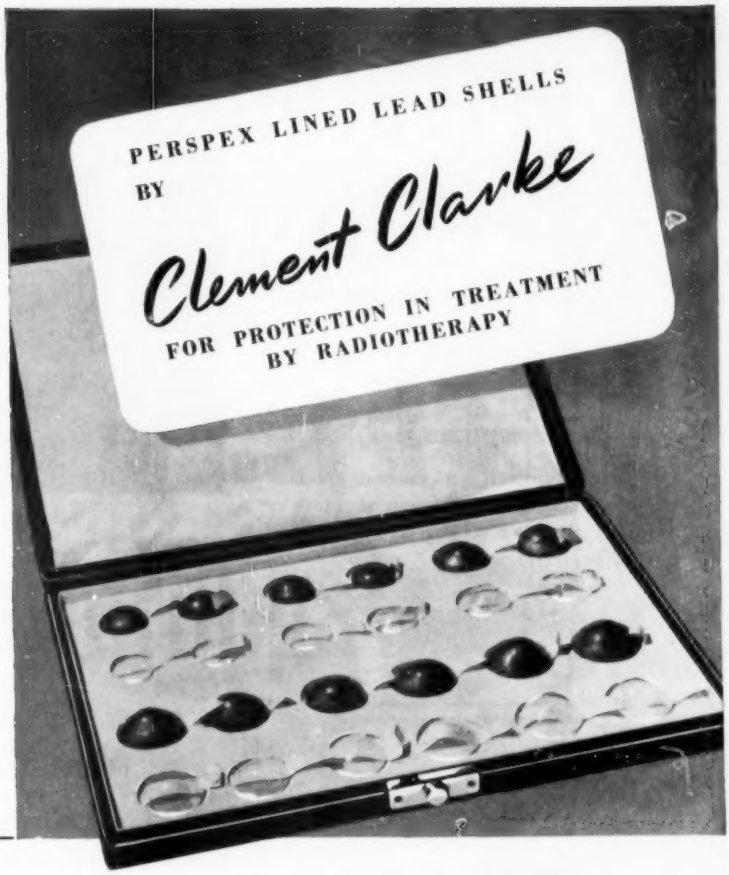

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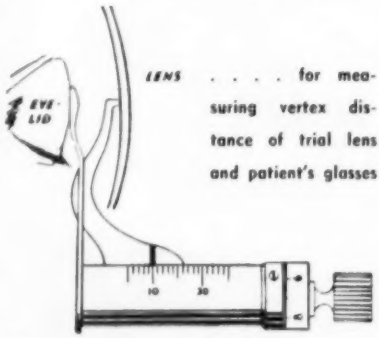

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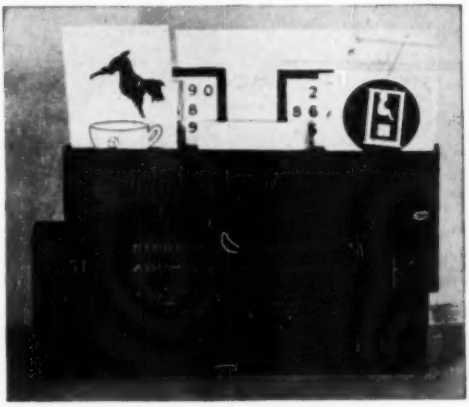

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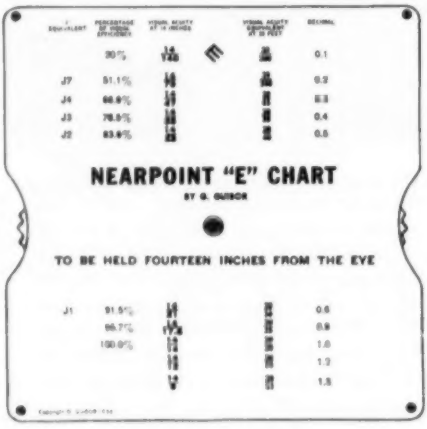

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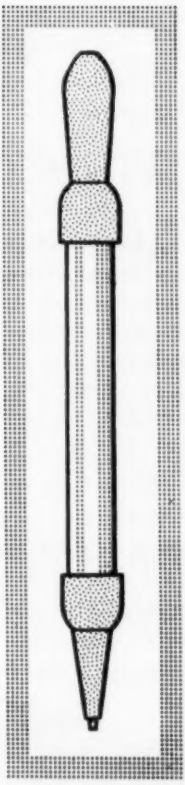

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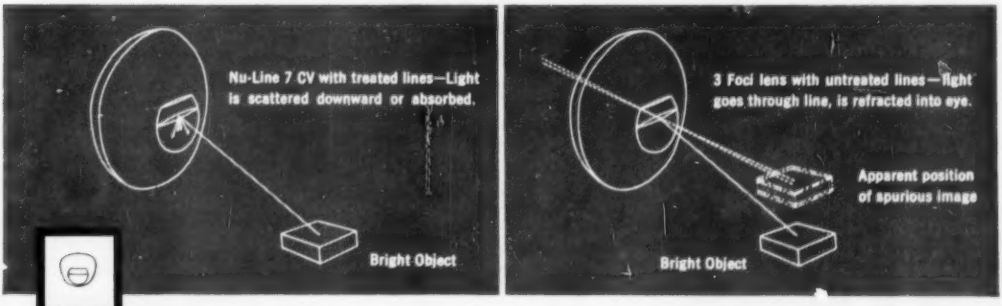
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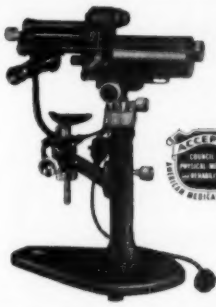

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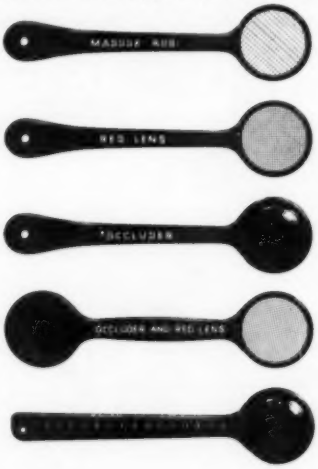

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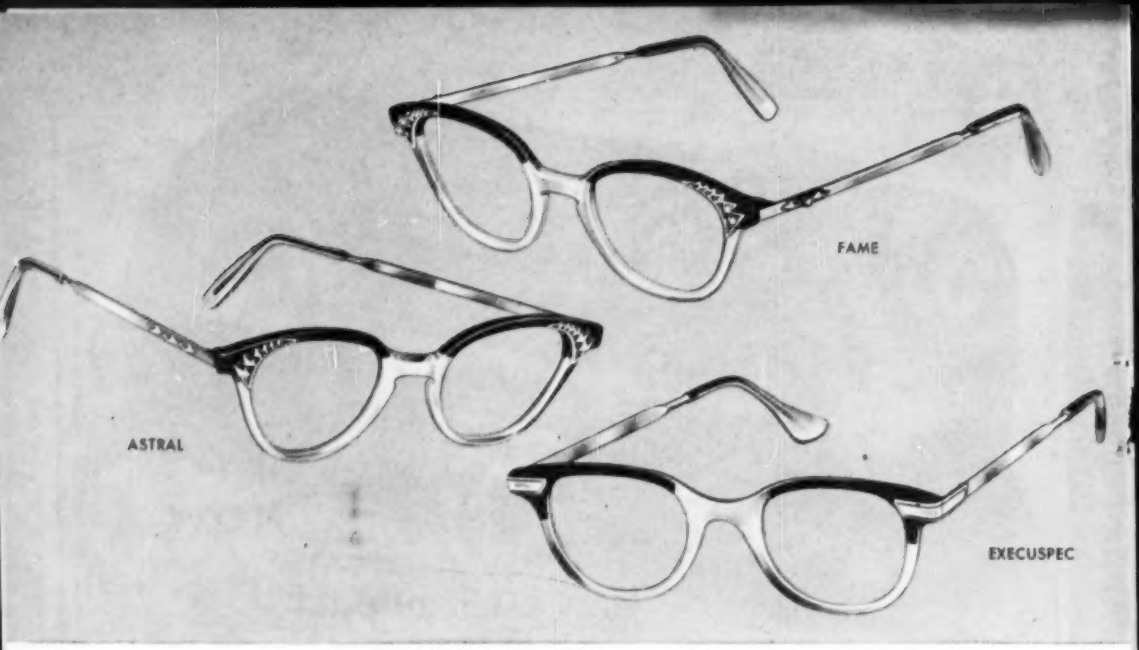

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CLASSIFICATION AND TREATMENT OF HEREDITARY CORNEAL DYSTROPHIES

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GENEVA, SWITZERLAND

AS A RULE hereditary degenerations of the cornea can be clearly distinguished from other corneal affections by their bilateral aspect, more or less typical morphology, and slow progression, with absence of vascularization. In addition, the fundamental criteria of all heredodegenerations apply equally to corneal degenerations: onset at approximately the same age in the different members of the family (homochronicity) and intrafamilial constancy of corneal alterations and of their evolution. However, their delimitation with regard to congenital malformations and certain inflammatory states is not always as simple as one would think, even when their characteristics have been quite clearly defined.

In fact, certain forms of interstitial keratitis, especially Hutchinson's keratitis, may be practically avascular, a feature which explains why certain infantile forms of corneal degeneration have been mistaken for manifestations of congenital syphilis. On the other hand, secondary vascularization in familial corneal degenerations is sometimes found, owing either to a chronic irritative state in relation to the epithelial alteration or to a coincidental band keratitis (scrofulous or other).

In addition, it must be stressed that certain corneal degenerations following inflammatory states of the anterior segment, injuries, operations, and glaucomatous states may, in all clinical aspects, simulate certain essential degenerations. This is particularly true of senile and presenile degeneration.

The classical forms of familial degeneration of the cornea are, in general, clearly progressive, leading to a decrease in visual acuity at a certain age and eventually causing a more or less total incapacity for work, an aspect which explains their social importance.

If we wish to classify the hereditary degenerations of the cornea, we must take into account the fact that the responsible mutations of the genes not only can produce numerous intermediary forms, but can create new types, which we must be able to fit into the classification without being obliged to change the way in which it is set up.

Furthermore, the existence of a series of general constitutional conditions which can cause changes of a degenerative type in the cornea must be considered when we establish a classification of the essential degenerations of the cornea.

We ophthalmologists are in a very advantageous position as compared with investigators in other branches of medicine, since the biomicroscope permits us not

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Professor, Clinique ophtalmologique.

Presented at the Postgraduate Course in Ophthalmology, Walter Reed Army Medical Center, Washington 12, D. C., May, 1953.

only to make a detailed analysis of the morphological changes in the cornea, but also to localize them with precision, according to the different layers of the cornea. Thanks to keratoplasty, it is possible to verify anatomically the exact nature of lesions observed and, at the same time, to control the authenticity of our clinical classification.

It will be seen that for the classical forms of familial degeneration of the cornea the histopathological control corroborates to a surprising degree the conception we based on biomicroscopical examination.

*Classification of the Heredofamilial Degenerations of the Cornea**

I. Parenchymatous degenerations
- A. Classical forms (noncongenital, progressive)
  - 1. Dominant forms
    - (*a*) Granular degeneration
    - (*b*) Lattice-like degeneration
  - 2. Recessive form: Macular degeneration
- B. Congenital forms (more or less stationary)
  - 1. Recessive form
  - 2. Dominant form
- C. Diverse forms
  - 1. Crystalline degeneration
  - 2. Primary fatty degeneration
  - 3. Primary calcareous degeneration (?)
  - 4. Cornea farinata
  - 5. Dystrophia filiformis profunda

II. Degenerations of the limiting membranes
- A. Anterior limiting membrane
  - 1. Recurrent hereditary erosions
  - 2. Juvenile epithelial degeneration (Meesmann's type)
  - 3. Juvenile degeneration of Bowman's membrane with epithelial changes
  - 4. Whorl-like corneal opacities (cornea verticillata)
  - 5. Mosaic-like ("crocodile-shagreen") degeneration
  - 6. Band-shaped degeneration
  - 7. Marginal degeneration
- B. Posterior limiting membrane
  - 1. Cornea guttata
  - 2. Polymorphous posterior degeneration

III. Combined forms (parenchyma and limiting membranes)
- A. Diverse combined forms
- B. Edematous dystrophies of the cornea
  - 1. Primary or essential edema of the cornea
  - 2. "Epithelial" degeneration of Fuchs

IV. Corneal degenerations in general affections
- A. Disturbances of lipid metabolism
  - 1. Lipochondro-osteodystrophy of Hurler
  - 2. Hand-Schüller-Christian disease
  - 3. Diverse affections
- B. Disturbances of intermediary protein metabolism
  - 1. Cystine diathesis
  - 2. Diverse affections
- C. Cutaneous affections
- D. Diverse affections

* Table by Franceschetti and Forni,[1] (slightly modified).

I. PARENCHYMATOUS DEGENERATION

A. Classical (Noncongenital, Progressive) Forms

The credit goes to Bücklers (1938) for having introduced into the classification of familial degenerations of the cornea a new criterion, the hereditary factor. On the basis of previous literature and numerous personal observations, he was able to show that the classical forms fall into three main groups. Two of these, the granular form (Type I of Groenouw) and the lattice-like form (Biber, Haab, Dimmer), are transmitted in the dominant mode. The third group, represented by the macular form (Type II of Groenouw), is inherited recessively.

Our classification,[1] based on these conceptions, has the great advantage of eliminating a certain lack of clarity which is frequently found in the literature. Indeed, authors who speak of nodular dystrophy, or Groenouw's disease, generally do not distinguish between Type I of Groenouw, which Bücklers has rightly called the granular form with dominant heredity, and Type II of Groenouw, or macular degeneration with recessive heredity. One should now give up the term Groenouw's disease, or nodular degeneration, which no longer corresponds to present knowledge,

and reserve the name nodular dystrophy for the nonhereditary condition described by Salzmann, in which nodules exist in the true sense of the word.

Using as a basis the facts I stated at the beginning, I shall briefly recall the essential characteristics of the three classical forms.

1. *Dominant Form.*—(*a*) Granular Form (Type I of Groenouw; crumb type): The granular form is characterized by the presence of whitish opacities in various forms (rings, arcs, garlands, disks, club-shaped forms, dots, and half-moons), the involvement ranging from a disciform area in the center of the cornea to the extent of two-thirds of the corneal depth.

The fact that the opacities are sharply delimited and included in the clear substance is characteristic. The peripheral area, as well as the deep layers of the cornea as a whole, remain untouched.

This form generally begins in the first decade of life. At the age of 5 years small dots and radial lines can already be discovered with the slit lamp. In general, the decrease in vision is not as great as in other classical forms and often does not prevent the patient from working, even at an advanced age. My colleagues and I recently found a case of typical granular dystrophy in a 27-year-old woman who presented no subjective symptoms and who merely came to change the glasses she wore because of myopia, as her vision was normal after correction.

However, in some families the vision may be gradually diminished after the age of 20 to 30. The sensibility may be nearly normal or definitely decreased. In the young the surface of the cornea is generally smooth; in the older patient it is slightly irregular.

Recurring erosions, resulting from epithelial alterations, may be observed in certain families, as well as in other forms of hereditary corneal degenerations. The granular form generally occurs in several successive generations; it is therefore a dominant character. One should not forget that isolated cases are frequent as a consequence of spontaneous mutations. When the characteristic corneal lesions are taken into account, diagnosis is easy and has a practical importance, as 50% of the descendants risk inheriting the corneal dystrophy.

(*b*) Lattice-like or Reticular Degeneration (Biber, Haab, Dimmer): The parenchyma shows a slight, diffuse clouding. Halfway between the center of the cornea and the limbus, typical lattice-like lines are seen, sometimes radial, sometimes running in all directions. They can be found in the various layers of the parenchyma but never reach the limbus. Sensibility is clearly diminished. Inflammatory attacks are often the first manifestation of the affection, which generally begins toward the end of the first decade of life.

Vision diminishes progressively, not only because of the opacities but also because of the irregularity of the corneal surface; and between the ages of 40 and 60 these patients become incapable of continuing their occupation. This condition has often been observed in several successive generations and therefore is also of the dominant type.

2. *Macular Degeneration* (Type II of Groenouw, Fehr).—This form begins between the ages of 5 and 9 years with a slight clouding of the parenchyma. Later on appear small and large, more or less confluent spots, with poorly delimited borders. The surface and thickness of the cornea become irregular. In advanced cases one

frequently finds larger, thickened spots, corresponding to the so-called nodules of Groenouw; this explains why certain authors have classified similar cases under the granular form.

The morphology of the figured elements, presenting a large intrafamilial and interfamilial variation, does not of itself permit a definite diagnosis. It should be emphasized that the diagnosis depends, above all, on the extension of the diffuse opacity to the periphery and to Descemet's membrane. Very characteristic is the presence of localized opacities near Descemet's membrane in the periphery of the cornea.

The sensibility is often diminished, and painful attacks associated with photophobia are observed, owing to recurrent erosions. Contrary to Bücklers' idea, I must insist that neither the state of corneal sensibility nor the presence of recurrent erosions enables one to distinguish the granular from the macular form, since in

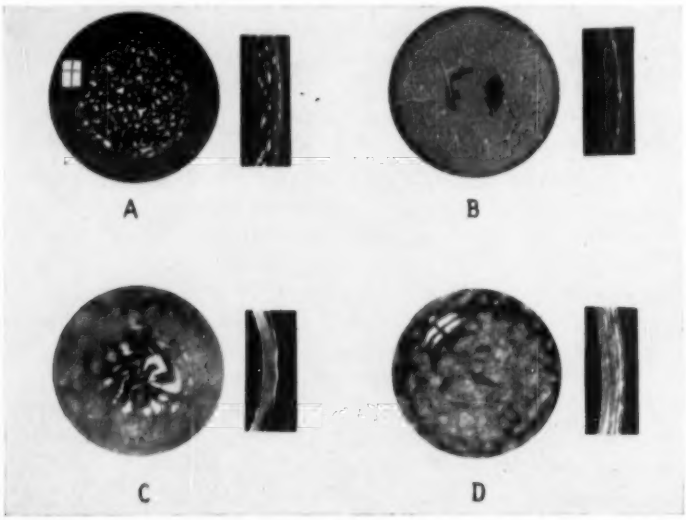

Fig. 1.—Classical forms of heredofamilial degenerations of the cornea. *A*, granular degeneration; *B*, lattice-like degeneration; *C*, macular degeneration; *D*, congenital form.

both types one finds cases with either normal or diminished sensibility, as well as families either affected or not by erosions.

In macular degeneration the diminution of vision leads in general to practical blindness between the ages of 30 and 40.

As the inheritance in this form is of the recessive type, consanguinity of the parents in affected siblings or isolated cases is frequent.

B. Congenital Forms (Slow Evolution)

Congenital opacities of the cornea of the malformative type have been known for a long time (Fig. 1).

In 1943 I called attention to the existence of a special form of diffuse opacity of the cornea, which is, as a rule, already present at birth. The following factors led me to distinguish this diffuse opacity of the cornea from other congenital opacities

of the malformative type and to place it in the large group of heredofamilial degenerations. Although in the majority of cases their presence from the time of birth had been ascertained, these opacities have, nevertheless, an evolutionary character, though manifested in an extremely slow fashion.

It must be mentioned that most frequently the congenital form presents a striking resemblance morphologically to the macular form of familial corneal dystrophy. Unlike the opacities of the malformative type, this condition is, so to speak, always bilateral and symmetrical; moreover, the familial character is very pronounced.

Cases of this type will be found in the literature under various names, such as congenital opacities of the cornea, intrauterine parenchymatous keratitis, and early interstitial keratitis.*

In the majority of cases two or more siblings are affected, while the parents are exempt but are often consanguineous. A recessive heredity is thus indicated.

There are rare observations in the literature suggesting a dominant inheritance. Unfortunately, we do not yet possess results of historical examinations concerning the dominant form, but, in view of the analogy with the recessive congenital form, it seems justifiable to distinguish it from pure malformations. Together with Jean Babel,[2] I have been able to show that the histological findings are in accordance with the clinical classification.

The group of the dystrophies with dominant heredity, with its two clinically very distinct granular and lattice-like types, microscopically shows similar lesions: destruction of the corneal lamellae, with deposits of intralamellar and extralamellar strongly basophilic granulations (Gram or May-Grünwald-Giemsa stain), corresponding to the clinical picture. The hyalinosis in the lattice-like type is deeper than in the granular form.

In the recessive macular degeneration, which clinically is more difficult to distinguish from the granular form, the histological lesions are entirely different.

It is not the disintegration of the lamellae, but a diffuse alteration of the cells at all levels of the cornea, that dominates the picture. Intracellular granulations are found both in the epithelium and in the fixed cells of the stroma. These refringent granules, not stainable with Sudan, show tinctorial characteristics which relate them to elastin (Weigert's resorcin-fuchsin stain).

Finally, in the congenital form there is neither hyalinosis nor the overabundance of the fixed cells, but a diffuse edema of the stroma with intralamellar granulations (Mallory stain). Thus, the histological findings support the classification of corneal dystrophies based on clinical and genetic considerations.

C. Diverse Forms

From the classical dystrophies must be separated various forms, which also affect the parenchyma but which present special characteristics. These opacities generally have a particular morphology. Often the vision is only slightly affected.

1. *Crystalline Degeneration.*—This form is incontestably of a heredofamilial character, the transmission being dominant. The opacities are localized in the

* Knowledge of this congenital form of hereditary dystrophy of the cornea is especially important, since there is always a risk of its being attributed to congenital syphilis, with unfortunate economic, moral, and social consequences for the patient.

anterior layers of the parenchyma directly under Bowman's membrane and are composed of innumerable small bright crystals in the form of needles of a whitish or a reddish-green color. The degeneration begins very early in the form of a central disk; progression is very slow, and the decrease of vision is not very marked. According to Malbrán [3] (1953), the deposit seems to consist of neutral fats, also visible in the enlarged Bowman membrane. In America, Fry [4] (1950) described hereditary and nonhereditary forms of crystalline degeneration.

2. *Primary Fatty Degeneration of the Cornea.*—This is a chronic unilateral or bilateral condition with late manifestation, frequently progressive, frequently with discrete irritative and recurrent attacks, and secondary vascularization. Yellow parenchymatous opacities, either diffuse or localized, are noted in the center or periphery of the cornea. Certain authors also believe that this is a secondary adiposis consequent on a torpid anterior uveitis; it seems more probable that it represents a special form of dystrophy. It is true that a familial character is almost always absent. There exists also a juvenile form of primary fatty degeneration, as shown by the case published by Orzalesi in 1947.

3. *Primary Calcareous Degeneration of Axenfeld.*—Of this form, which according to Walsh and Howard (1947) may affect the conjunctiva and the cornea, no familial cases are known.

4. *Cornea Farinata.*—This is a very delicate clouding composed of fine dots, localized especially in the deeper layers of the cornea. It was described by Vogt in 1923 as a senile or presenile corneal alteration, but a few observations in the literature show that this affection may have a hereditary character.

5. *Dystrophia Filiformis Profunda Corneae* (Maeder-Danis).—In a case of abortive keratoconus of the right eye and typical keratoconus of the left eye, we observed in the deepest layer of the cornea of the latter a disk-like opacity, composed of filaments entangled in a corkscrew manner. As no similar cases are known, it is, of course, not possible to prove that the condition is a heredofamilial degeneration, but the very particular localization and the association with keratoconus, the hereditary character of which cannot be doubted, speak in favor of this idea.

II. DEGENERATIONS OF THE LIMITING MEMBRANES

A. Anterior Limiting Membrane

1. *Recurrent Hereditary Erosions.*—In 1928 I had the opportunity of examining a family with recurrent hereditary erosions in six successive generations. The disease generally became manifest at the age of 4 to 6 years, usually after a small corneal trauma. With age these attacks, which generally occurred in the morning, became rarer and less intense.

2. *Juvenile Epithelial Degeneration.*—In 1932 Meesmann drew attention to the existence of a special form of juvenile epithelial degeneration in which he observed a local excess of glycogen.

The changes, localized in the epithelium and sometimes also in Bowman's membrane, are visible only with the slit lamp. They are fine, punctiform opacities with the aspect of vesicles and droplets in reflected light. Since then similar cases have been published, confirming its hereditary character; but, unfortunately, there is no histochemical examination confirming the glycogenic nature of these lesions.

3. *Juvenile Degeneration of Bowman's Membrane.*—This curious form of hereditary degeneration, associated with epithelial changes, was described by Reis, in 1917, and later by Bücklers, in 1949. With the slit lamp the opacities seem to be composed of gray delicate figures in the form of a geographic map. The epithelium shows changes and may present erosions and ulcerations similar to a certain degree of neuroparalytic keratitis.

In 1953 Gruber [5] of Zurich published the history of a family in which several members of a sibship showed various stages of this affection; the less severe forms were very similar to the juvenile epithelial degeneration of the Meesmann type, showing that the two forms are closely related.

4. *Whorl-like Corneal Opacities.*—Fleischer described these in 1910. Three familial cases of this rare condition appear in the literature. Gruber, who has observed two families, thinks that it is a congenital anomaly and proposes the name cornea verticillata. An anatomical examination made by Vogels, in 1934, revealed the presence of granules of a glycogenic nature under the epithelium.

5. *Anterior Mosaic-like Degeneration.*—This was described by Vogt in 1930 as a senile alteration under the name of "crocodile shagreen." Valerio (1919, 1942) observed a juvenile form of mosaic-like degeneration in a youth of 17, whose father presented a primary bilateral band-shaped degeneration of the cornea. The different aspects in father and son may depend on the age of manifestation. As yet, no histological examination is known, but I had the opportunity of examining a case of anterior mosaic-like degeneration following a traumatic keratitis with hypopyon. I was able to carry out an histological examination which revealed that the presence of ruptures in Bowman's membrane was the basis of this curious condition.

6. *Band-Shaped Degeneration of the Cornea.*—This is in general secondary to glaucoma, chronic iridocyclitis, and hypercalcemia (Cogan and associates [6]) and is seen especially in the child as a result of chronic polyarthritis, or Still's disease. Nevertheless, primary band-shaped degeneration showing a familial character is known.

7. *Marginal Degeneration or Marginal Ectasia of the Cornea.*—This condition does not seem to be familial in spite of its degenerative character. The same is true of Vogt's "white limbus girdle," but sometimes it is associated with corneal degenerations whose familial character cannot be doubted (Schnyder, 1939).

B. Posterior Limiting Membrane

1. *Cornea Guttata.*—Dystrophy of the corneal endothelium was described by Stähli in 1920 as a "bedewing" of the endothelium, and later by Vogt as cornea guttata. According to Goar (1934), it occurs in some degree in about 6% of persons over 20 years of age. It usually begins in the fourth or fifth decade and is three times as common in women as in men. It is characterized by the presence of droplets on the posterior limiting membrane, especially visible with reflected light or on examination of the zone of specular reflection. Usually the endothelium is more or less covered by pigmented deposits. Familial cases have been observed.

2. *Polymorphous Degeneration.*—This is a rare form characterized by the presence of slight concavities, vesicles, and polymorphic opacities of the posterior limiting membrane. Forni (1949) observed this form of degeneration in a man of 29 and his daughter, of 4 years (Fig. 2).

III. COMBINED FORMS

A. Diverse Forms

We have already pointed out that in the classical forms of heredofamilial degeneration, especially in the macular form, not only the anterior limiting membrane, but also the posterior limiting membrane, may be involved. On the other hand, degenerations of the limiting membranes may produce alterations of the corneal parenchyma.

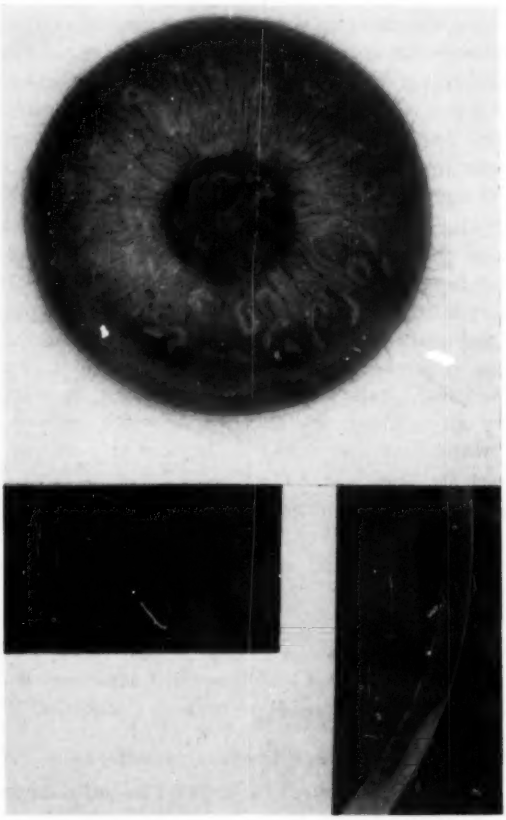

Fig. 2.—Posterior polymorphous degeneration of the cornea (personal observation, published by Forni, 1949).

B. Edematous Dystrophies of Cornea

The essential feature of the edematous dystrophies of the cornea is the thickening and secondary diffuse clouding of the corneal parenchyma. The best-known condition in this group is the epithelial degeneration of Fuchs, but I agree with Calhoun [7] (1951) that Fuchs's degeneration is only a late state of edematous dystrophy, characterized by secondary epithelial degeneration.

It should be emphasized that in all dystrophies of this type the first alterations will be found in the endothelium as pronounced cornea guttata. In the last several

years I have had the opportunity of examining various patients showing different degrees of edematous corneal dystrophy.

1. *Chronic Intermittent Primary or Essential Corneal Edema.*—Aubineau, in 1922, after having recalled an observation by Despagnet, drew attention to the primary chronic edema which occurs particularly in the adult. The visual disorder is periodic, owing to an intermittent or cyclic edema, generally intense in the morning and disappearing toward evening. The vision is greatly diminished in the morning and may become almost normal toward evening. Hänmerli (1936) was able to show that the edema appeared in the evening and disappeared toward morning when the patient worked during the night and slept during the day. In the more advanced cases the epithelium shows a steam-like opacity with vacuoles, especially in the central area of the cornea.

Figure 3 shows such a condition in an elderly woman who had for many years recurrent edema of the cornea and who now presents the first stage of Fuchs's epithelial dystrophy.

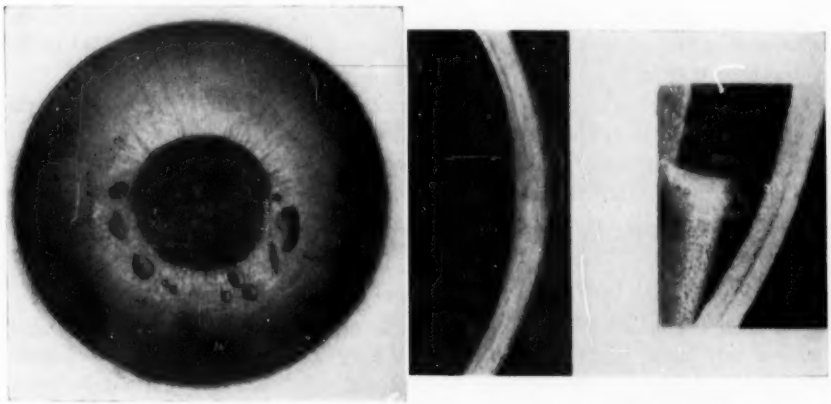

Fig. 3.—Chronic intermittent corneal edema, with beginning Fuch's epithelial dystrophy (personal observation).

2. *Fuchs's Epithelial Dystrophy with Lesion of the Parenchyma and Typical Cornea Guttata.*—This form is often difficult to distinguish from the secondary form of Fuchs's degeneration, which is very similar morphologically and clinically and which is sometimes seen after an intraocular operation, glaucoma, or chronic iridocyclitis. The diagnosis is still more difficult in that Fuchs's degeneration may be complicated by glaucoma. Familial occurrence in the primary form of edematous dystrophies has been observed several times, showing that a genetic factor plays an important role.

IV. CORNEAL DEGENERATIONS IN GENERAL AFFECTIONS

I should like to mention only the most important forms of corneal degenerations associated with general affections.

A. Lipid Metabolic Disorders

1. In lipochondro-osteodystrophy of Hurler's type, or gargoylism, corneal opacification will be found in about 70% of all cases.

This congenital condition is characterized by skeletal alterations, which result in a disproportioned dwarfism. The head, which is already large at birth, sits on a disproportioned body; the neck is very short; the thoracic cage is frequently barrel-shaped, with marked kyphosis; the abdomen is large, and there is pronounced hepatosplenomegaly. The cornea presents a diffuse, rather uniform cloudiness of the whole parenchyma. The histological picture shows dissociation of the lamellae, especially a replacement of Bowman's membrane by large cells loaded with lipids.

2. Hand-Schüller-Christian disease may exceptionally present corneal complications.

3. Furthermore, we must mention fatty dystrophy of the cornea in idiopathic hyperlipemia (Dunphy, 1950), or general xanthomatosis.

B. Disorders of Intermediary Protein Metabolism

In this group, it is the cystine diathesis which plays an important role.

Bürki, of Basle, was the first to describe, in 1941, corneal alterations in a case of cystinuria. Since then several cases have been observed. The corneal opacity is composed of innumerable brilliant yellowish-white dots, regularly distributed in the anterior part and rarely through the whole cornea. Only the posterior third of the central area may be free.

Bürki was able to carry out anatomical examinations and to demonstrate the presence of cystine crystals in the conjunctiva, cornea, iris, and choroid. Consanguinity is frequent in cystine diathesis. A recessive heredity is therefore probable.

Considering the importance of corneal alterations in the diagnosis of cystine diseases, the need for systematic slit-lamp examination in all cases of dwarfism and, in particular, of renal rickets, cannot be too strongly stressed.

C. Cutaneous Conditions of Hereditary Type

Of such conditions which may be accompanied by corneal alterations, I shall mention only ichthyosis, hyperkeratosis, and keratoma palmare et plantare hereditarium, especially the recessive form. Exceptionally, corneal changes may be found in anhidrotic ectodermal dysplasia and in Rothmund's syndrome (infantile sclero-poikiloderma with cataract) and in atopic dermatitis, as shown recently by Hogan.[5]

TREATMENT OF HEREDOFAMILIAL DEGENERATIONS OF CORNEA

One may say that the whole arsenal of ophthalmological therapeutics has been applied in the treatment of heredofamilial degenerations of the cornea: internal tuberculin therapy, antisyphilitic treatment, subconjunctival injection of chloride or cyanide, diathermy, ultraviolet radiation and x-rays, hormones, and vitamins have been tried, without notable success.

In the case of band-shaped degeneration, abrasion of the cornea and application of hydrochloric acid or ethylenediamine tetraacetic acid (EDTA) may give satisfying results (Grant [9]).

We have been surprised to see that anesthetics, especially Larocaine, may favorably influence the corneal clouding in the early stages of Fuchs's dystrophy.

As for the surgical treatment of the classical forms of corneal dystrophies, it is interesting to note that Usher, as well as Stanka, insisted that eyes presenting dystrophic alterations of the cornea were not suitable for corneal grafts.

The idea that corneal degeneration might be related to trophic disorders may possibly have prevented the application of keratoplasty in these cases over a long period of time. Together with Kiewe, I showed in 1936 that the pessimism concerning keratoplasty in the case of corneal dystrophies was not justified. Since then, numerous authors have confirmed this statement. In the granular form of corneal dystrophy a lamellar graft may give favorable results.

In the lattice-like form, Paufique obtained good results with deep lamellar grafting. For the macular and the congenital forms perforating keratoplasty is indispensable for a good visual result.

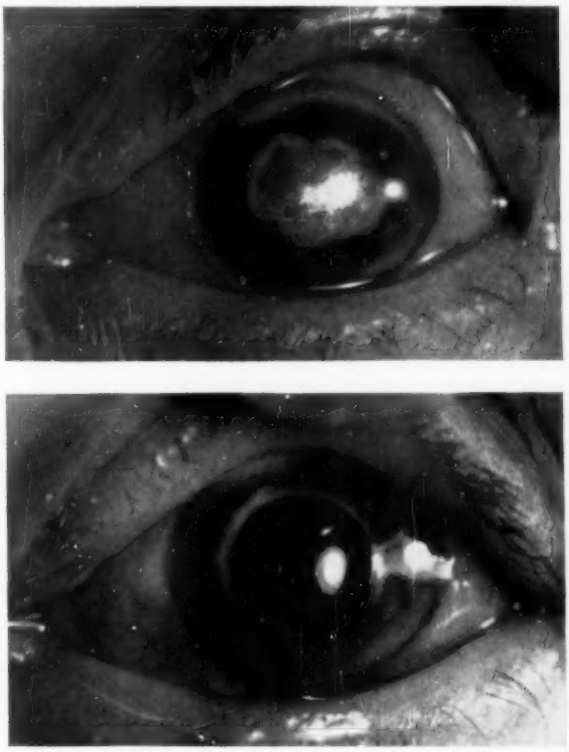

Fig. 4.—Fatty degeneration of the cornea before and after keratoplasty (personal observation).

It is the same for Salzmann's nodular dystrophy, which is not hereditary, but in general secondary to infantile phlyctenular keratitis.

In the different forms of degeneration of the anterior limiting membrane, lamellar keratoplasty is indicated when the vision is unsatisfactory.

In the primary fatty degeneration of the cornea, which generally produces an important diminution in visual acuity, the prognosis for keratoplasty in general is not very favorable. Nevertheless, in two cases we obtained good results with perforating keratoplasty (Fig. 4). Fuchs's epithelial dystrophy has been classed, with

reason, among the most unfavorable forms for grafting, whether lamellar or perforating grafts. According to Paufique, the results of perforating keratoplasty in Fuchs's dystrophy seem to be better if it is preceded by complete abrasion of the endothelium.

On the basis of our experience, we can assert that the mushroom graft has greatly improved the prognosis of keratoplasty in Fuchs's dystrophy. The results are often disappointing, even with this method; but in several cases we obtained a useful amelioration of vision, which is the more appreciable as these cases are generally found in elderly persons, not infrequently with aphakia.

As regards the surgical treatment of hereditary corneal dystrophies, we can affirm that today the prognosis is much better than in 1922, when Treacher Collins, concluding his report on the ocular abiotrophies before the Ophthalmological Congress in Washington, stated that "the trephining of the superficial layers of the cornea for hereditary nodular opacities might at times produce a slight improvement of sight."

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PLATYBASIA AND THE ARNOLD-CHIARI MALFORMATION

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PLATYBASIA and the Arnold-Chiari deformity are of concern to the ophthalmologist. Not only are the ocular signs and symptoms of these entities often the presenting complaints but, equally important, they simulate those of multiple sclerosis, tumor of the brain stem or cerebellum, and other lesions of the posterior fossa, which have an entirely different prognostic and therapeutic significance. Since these conditions have not received general recognition in the ophthalmological literature,* it will be the purpose of this communication to describe the abnormalities as represented in the pertinent literature and to present several cases studied by us with emphasis on the ophthalmological aspects.

The abnormality variously called platybasia, flat skull, or basilar impression consists of an upward bulge or invagination of the occiput in the region of the foramen magnum.† There is usually a partial fusion of the upper cervical vertebrae to the skull and to each other, with a protrusion of the odontoid process of the axis into the posterior fossa. The neurologic and neuro-ophthalmologic symptoms are due in part to the encroachment on the volume of the posterior fossa and to the impingement of the odontoid process on the brain stem and cerebellum. The bony anomaly is usually congenital but gives the impression that the skull has been forced down onto the cervical spine. The only certain way of making the diagnosis is by roentgenographic visualization or anatomic inspection. The arching of the occiput and the high position of the odontoid process are pathognomonic of the anomaly.

The Arnold-Chiari deformity consists in a herniation of part of the cerebellum (the so-called cerebellar "tonsils") and medulla through the foramen magnum. The symptoms are much like those in platybasia, inasmuch as there is compression of the brain stem and cerebellum in both instances. Indeed, the two conditions often coexist. Hence they are properly considered together from the clinical point of view.

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* Walsh [1] appears to be the only one who has given a description of the abnormalities in the ophthalmic literature.

† Strictly speaking, platybasia is an anthropological term referring to a flattening of the clivus in respect to the skull, while basilar impression refers to a protrusion of the base of the skull into the posterior fossa; but the names are used interchangeably for the clinical anomaly here described.

Unlike platybasia, there is no characteristic bony abnormality in the region of the foramen magnum with the Arnold-Chiari deformity, but there is often an associated meningomyelocele or spina bifida.

The skull changes of platybasia were first described in 1876 by Virchow,[2] who considered them to result from rickets, osteomalacia, or senile atrophy. That the anomaly could be responsible for neurologic symptoms was first pointed out by Homén [3] (1901), who called attention to the pressure of the odontoid on the medulla. The crucial significance of x-rays in making the diagnosis was first noted by Schüller [4] (1911), but precisely defined only at a much later date, by Chamberlain [5] (1939) and Bull [6] (1951) (Fig. 1).

The accelerated interest in the anomaly during the past two decades has been due in part to the appreciation of the x-ray criteria for making the diagnosis and

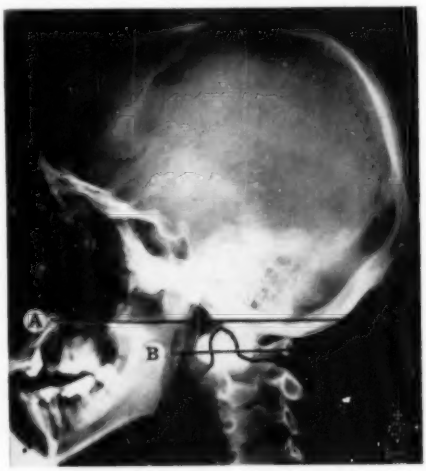

Fig. 1.—Lateral view of normal skull taken to show base and first three cervical vertebrae. Chamberlain's line [5] (*A*) extends from the hard palate to the foramen magnum. Bull's line [6] (*B*) is drawn through the plane of the atlas (first cervical vertebra). Normally these two lines are approximately parallel. The odontoid process of the axis (second cervical vertebra) has been outlined. Normally the entire odontoid process lies below Chamberlain's line.

in part to the introduction of surgical decompression for its treatment. The first report of a surgical approach for platybasia is that of Ebenius [7] (1934).

The first authentic case of the Arnold-Chiari deformity was apparently reported by Arnold [8] (1894), occurring in association with spina bifida and hydrocephalus. The following year Chiari [9] reported a series of similar cases which he had studied independently. The association with meningomyelocele and spina bifida was subsequently shown by numerous reports (Russell and Donald [10]; Ingraham and Scott,[11] and others) and formed the basis for the "traction theory" of its pathogenesis, by which the spinal evaginations were believed to pull the cerebellum and brain stem into the cervical canal (Penfield and Coburn [12]; Lichtenstein [13]). However, these spinal anomalies are not invariably present with the Arnold-Chiari deformity, and it is just such cases that give rise to the problem in differential diagnosis. ‡ The

‡ References 14, 15, and 16.

value of myelography in demonstrating the herniation of the cerebellar "tonsils," with the resultant obstruction at the upper end of the cervical cord, was pointed out simultaneously by List [17] and by Adams, Schatzki, and Scoville.[18] Finally, a method for decompression of the base of the skull and upper cervical segments was introduced (Aring [16]; Penfield and Coburn,[12] and McConnell and Parker [14]) and is now indicated when the symptoms are persistent and sufficiently disabling.

The signs and symptoms of platybasia and the Arnold-Chiari syndrome are due in part to direct involvement of the cervical nerves and in part to compression of the brain stem and cerebellum, with the attendant obstruction of the cerebrospinal fluid. Attacks of nuchal pain, described as "stiff neck," are common, often precipitated by coughing, sneezing, and straining or by turning of the head. The neurologic manifestations are characterized chiefly by ataxia, spasticity of gait, numbness in extremities, and dysphagia.§ Headaches are also frequent, being described as either occipital or frontal. Lumbar puncture often reveals a block in the cerebrospinal fluid dynamics, with consequent elevation of the total protein content. With platybasia a short neck, giving rise to a hunched-up appearance ("bull neck"), may suggest the anomaly, while with the Arnold-Chiari deformity the associated presence of meningomyelocele or spina bifida is suggestive.

The one ocular sign that has repeatedly been noted is nystagmus; in fact, a survey of all the adult cases of the Arnold-Chiari deformity showed nystagmus to be second only to motor reflex changes in frequency.[21] The nystagmus is characteristically of the jerk type, being horizontal on looking to either side and vertical on looking upward. Diplopia is also a frequent complaint, but the basis for it has not always been apparent in the protocols; some cases have had a sixth nerve weakness, as might be expected with increased intracranial pressure. Less common is the complaint of blurred vision, and one patient with the Arnold-Chiari deformity was found to have a bitemporal hemianopsia.[1] Papilledema may, of course, occur with the cerebrospinal fluid block, but as has been noted several times, it appears to be less common with these deformities than with other conditions causing hydrocephalus.[18] Rarely, anisocoria, ptosis, and corneal anesthesia have been noted.[22]

REPORT OF CASES

CASE 1.—*Platybasia and Arnold-Chiari malformation, causing long-standing ataxia in man of 49; recent worsening, with neurologic signs pointing to involvement of pyramidal tracts and cerebellum; vertical and horizontal nystagmus, varying with posture; skew deviation. Suboccipital decompression with progression of symptoms and eventual death. Postmortem examination.*

F. D. (705748), a 49-year-old man, whose chief complaint on entry into the hospital was unsteadiness of gait of 25 years' duration but progressively worse during the preceding 3 years. The patient characterized his difficulty as stiffness of his legs and tendency to lose his balance. Several years previously he had been studied in another hospital, where a diagnosis was made of "primary cerebellar disease, type and cause unknown." The patient had had no headache, convulsions, speech difficulty, or visual disturbance.

Neurologic examination, aside from the eyes, showed hyperactive reflexes in the arms, spasticity of the legs, hyperactive ankle and knee jerks, bilateral extensor plantar responses, positive Romberg sign, spastic ataxia, and wide-based gait. The skull did not seem abnormal, but the patient had a short neck. Ocular examination showed the following: vertical nystagmus in the primary position of gaze, increasing on looking upward or downward, with the fast component

§ References 13 and 18 through 21.

in the direction of gaze, and horizontal nystagmus on gaze to either side. On tilting the head to the left a marked horizontal nystagmus developed, with the fast component to the left. The opticokinetic response was absent on rotation of the field to the patient's right but present on rotation to the left. Although no gross limitation of eye movements was apparent, there was a vertical diplopia simulating paresis of the right inferior rectus and left superior rectus. Ophthalmoscopic and visual field examination showed nothing abnormal.

Lumbar puncture showed normal dynamics and a total protein of 50 mg. per 100 cc.

The routine x-ray films of the skull were reported as showing nothing abnormal, but repeat films (Fig. 2) taken to visualize the foramen magnum region revealed the deformity of platybasia: "There is definite platybasia, with the tip of the odontoid lying approximately 2 cm. above the line drawn between the hard palate and the foramen magnum. The cervical spine shows accentuation of its normal lordosis, with slight degenerative changes about many vertebral bodies. The cervical spine otherwise is not grossly remarkable."

The patient had a suboccipital exploration and decompression, with removal of the occipital bone around the foramen magnum and the arches of the three upper cervical vertebrae. The Arnold-Chiari malformation was seen, with portions of the cerebellum extending down to the third cervical segment.

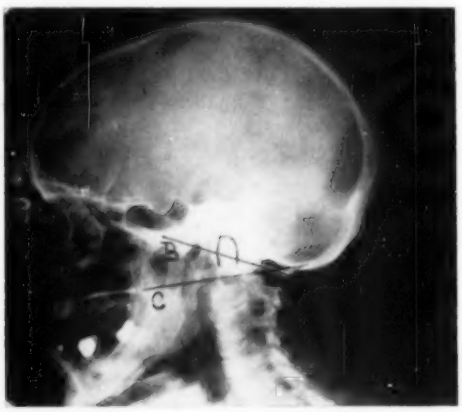

Fig. 2 (Case 1).—Lateral view of skull showing the x-ray abnormalities of platybasia. The odontoid process here extends above Chamberlain's line, and Bull's line transects Chamberlain's line near the foramen magnum.

During the first two postoperative weeks the patient continued to have profound ataxia and nystagmus. His pharyngeal and tracheal reflexes were noted to be depressed and considerable mucus collected in the trachea. He also apparently had a phrenic paralysis with atelectasis. On the 15th postoperative day the patient collapsed after getting out of bed and was temporarily unresponsive. Subsequently it was evident that the patient had absence of the gag reflex and inability to swallow, weakness of both trapezius and sternocleidomastoid muscles, and weakness of the left arm and leg. There was an extensor plantar response and sustained ankle clonus on the left. The patient showed mild improvement in the subsequent two weeks and was discharged from the hospital six weeks after the operation.

The patient was not seen again until five months later, when he was brought into the hospital, dead on arrival. The events leading up to this terminal episode could not be ascertained.

Postmortem examination of the head region showed, aside from the operative defect, an unusually small posterior cranial fossa, flattening and thickening of the clivus, and herniation of the cerebellar tonsils to the level of the third cervical segment. The medulla was elongated and compressed from side to side, and there was a conspicuous horizontal groove on its anterior aspect. Histologically, there was notable degeneration and reactive gliosis in the cerebellum and a recent necrosis and extensive microglial phagocytosis in the medulla. The findings were thought to be characteristic of a severe degree of the Arnold-Chiari malformation.

The vertical and horizontal nystagmus in this patient, and the skew deviation and asymmetry of the opticokinetic response, are ocular signs which may be found with any lesion of the posterior fossa. The variation of the nystagmus with posture is suggestive of the Arnold-Chiari deformity but is not pathognomonic, since tumors of the cerebellum can on occasion show the same variation. The duration of the symptoms, 25 years, without striking remissions, was perhaps more indicative of the correct diagnosis, but was not infallible evidence.

The fact that the routine skull x-ray was reported as negative is especially noteworthy in indicating how the anomaly may be overlooked if one does not take special lateral films to visualize the defect specifically.

CASE 2.—*Platybasia, producing "weak spells," tingling in the left arm, nystagmus, and diplopia. Decompression, followed by death. Postmortem examination.*

F. C. (780269), a 35-year-old man, who was admitted to the Massachusetts General Hospital because of "weak spells" which had occurred in the past few months. These were characterized

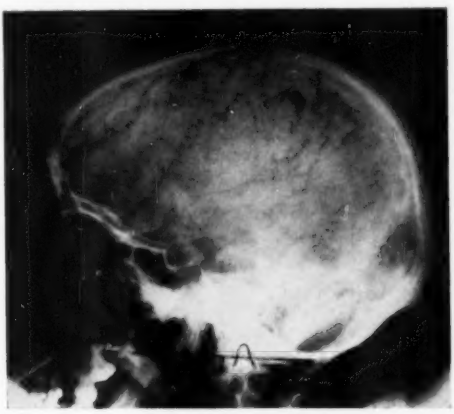

Fig. 3 (Case 2).—Lateral view of pneumoencephalogram (brow down). The atlas is fused to the occiput, and the tip of the odontoid process lies above Chamberlain's line.

by a ringing in the ears, followed by a feeling of generalized weakness, excessive sweating, feeling of heat, tingling sensation in the left arm, thickness of speech, and acute dizziness, with true illusory movement of the environment. He had had five such attacks prior to the hospital entry. Each attack lasted about one hour and was followed by a prolonged sleep of several hours. More recently he had noticed some up-and-down "jumpiness" of objects that he was fixating.

Neurologic examination revealed some reduction in pinprick sensibility of the left forearm as the only definite abnormality aside from the ocular changes. There was a vertical nystagmus in the primary position of the eyes, increasing on downward gaze, and a superimposed horizontal nystagmus on looking to either side. Vertical diplopia developed on gaze to either side, simulating weakness of both superior rectus muscles (skew deviation), and a horizontal diplopia, corresponding to a slight weakness of the left lateral rectus muscle. The opticokinetic response could not be elicited in the horizontal plane, and there was an inconstant ocular motor dysmetria.

The initial x-ray films of the skull were reported as showing nothing abnormal, but the pneumoencephalogram (Fig. 3) was reported as showing "a congenital malformation of the upper cervical region. The atlas appeared fused to the occiput. The tip of the odontoid process projected above Chamberlain's line. Appearance was that of platybasia."

A suboccipital craniectomy was done, with laminectomy of the first three cervical vertebrae. The patient did not rally from the ether anesthesia. The following day the wound was explored, and it was found that the cerebellum was under considerable pressure. A complete occipital craniectomy was done. Although the patient was placed in a respirator, he remained completely unresponsive and died five days after the operation.

Postmortem examination showed extensive swelling of the cerebral hemispheres, a bilateral temporal pressure cone, and widespread infarction of the cerebellum, midbrain, pons, and upper medulla, with conspicuous indentation of the dorsal surface of the medulla.

The ocular findings in this patient were extraordinarily important, since they were the only neurologic abnormality noted, aside from slight sensory changes in one forearm. They consisted of a jerk type of nystagmus in the horizontal and vertical planes. The vertical nystagmus was somewhat unusual, although not unique, in being most marked on downward gaze. The nystagmus, together with the skew deviation, absence of the opticokinetic response, and questionable ocular motor dysmetria, pointed to a lesion in the posterior fossa but gave no indication of what the true diagnosis was. The short duration of symptoms was not what one would expect with a congenital abnormality. As in the foregoing case, the routine skull x-rays were reported to show nothing abnormal, but special films revealed typical platybasia.

CASE 3.—*Platybasia and Arnold-Chiari malformation, with symptoms beginning at the age of 15, consisting of lethargy, staggering gait, nuchal pain, and blurring of vision. Symptoms exaggerated by hyperextension of head or by coughing. Incidental spina bifida. Suboccipital craniectomy with laminectomy of the atlas and axis. Recurrence of episodes of blurred vision, weakness, and pain in neck five years postoperatively, interpreted as hydrocephalic crises.*

R. F. (583262), a 24-year-old laborer, who was first seen at the Massachusetts General Hospital at the age of 18 with complaints of loss of ambition and unusual somnolence (three years), staggering of gait (two years), aching pain in nuchal region (one year), and blurring of vision and illusory "jumping" of the environment (four to five weeks). The last symptoms were usually worse on his first arising in the morning and could be brought on by coughing or by bending his head backward. Occasionally they were accompanied by numbness of his hands and incorrect use of words.

Neurologic examination, aside from that of the eyes, gave the following findings: Hyperextension of the head induced dizziness and blurring of vision. There was slight tenderness in the occipitonuchal angle. There was slight and symmetrical impairment in the finger-to-nose test. The gait was wide-based. The patient lost his balance when the eyes were closed and his head extended. The deep tendon reflexes of the left arm were absent, but the remainder of the reflexes were normal. There was hypalgesia in the segment corresponding to the second cervical segment, but sensation was otherwise normal.

The eyes showed a vertical nystagmus in the primary position of gaze, increasing on looking down and decreasing on looking upward. On gaze to either side a horizontal nystagmus was superimposed, with the fast component in the direction of gaze. There was a crossed diplopia on looking down and to the right and a homonymous diplopia on looking up and to the right but no vertical separation of the images. The visual acuity, fundi, and fields were normal. No accentuation of the nystagmus could be induced by hyperextension of the head.

X-ray showed moderate platybasia. The first cervical vertebra was smaller than normal, and the odontoid process extended several centimeters above Chamberlain's line. There was no evidence of atlanto-occipital ankylosis. Surprisingly, cervical myelography showed no filling defect. Films of the spine showed a spina bifida of the first sacral segment.

The patient had a suboccipital craniectomy and laminectomy of the atlas and axis. At operation an anomalous ring of bone was found extending down for approximately 1 cm. from the level of the foramen magnum. The cerebellar tonsils were found herniated down to the upper margin of the third cervical vertebra (Fig. 4).

Postoperatively, there was little objective change in findings for the few months that he was under observation, but the patient felt subjectively improved. However, he has had episodes of blurred vision recently (five years after the operation). These episodes occur several times a week and consist of sudden fuzziness of objects, lasting only a few minutes. They are accompanied by some weakness of the extremities and slurring of speech and are followed by pain in the neck, which may last a whole day. The patient has not been seen during these episodes, but they have been tentatively interpreted as hydrocephalic crises. Nevertheless, neurologic and neuro-ophthalmic examination at the present time shows no significant abnormality.

The neurologic, ophthalmologic, and roentgenologic signs and symptoms in this case were typical of platybasia and the Arnold-Chiari malformation. Although the lesion was undoubtedly congenital in origin, symptoms did not occur until adolescence, as is so often the case. The negative findings on myelography were surprising

Fig. 4 (Case 3).—View of the operative site after reflection of the dura mater. A portion of the cerebellum is evident in the upper left corner of the wound. Occupying most of the exposed field are the cerebellar "tonsils," covering the dorsal surface of the medulla. The conspicuous groove on the surface of the cerebellar tonsils corresponded to a ring of anomalous bone that was removed in making the exposure (photograph, courtesy of Dr. James C. White).

but only indicate that negative results are not conclusive. The visual complaint prior to operation and subsequently may well be due to the nystagmus, since the patient volunteered the statement that he had "jumping" of the environment. The accentuation of the vertical nystagmus on downward gaze, although unusual, was similar to that in the preceding case and in the case to follow.

CASE 4.—*Platybasia (and probably Arnold-Chiari malformation). Headaches with nausea in adolescence. Later, progressive incoordination, left-sided weakness, hypalgesia, nystagmus, and ocular motor dysmetria. Operative decompression, with slight worsening of symptoms.*

J. G. (397062), a 37-year-old mail clerk, who has been followed by the neurologic and neurosurgical service of the Massachusetts General Hospital for 10 years. He had an occipital decompression and upper cervical laminectomy at this hospital 10 years ago.

At the age of 8 years he began having severe headaches accompanied by nausea but no vomiting. These ceased spontaneously at the age of 17, but he then began to note persistent staggering and a tendency to veer to the left. He was particularly unable to walk along a log as others could do, and he stumbled on rough ground. At the age of 23 the fact that he had nystagmus was called to his attention, although he had no subjective visual complaint. At 25 years he began having a "stinging" sensation with a feeling of pins and needles in the left hand. This extended up the left forearm and was followed shortly by a tired feeling and weakness of the left arm and left leg and by a sensation of numbness in the left foot.

Despite the foregoing symptoms, the patient was inducted into the Army, but shortly thereafter he was hospitalized because of the weakness of the left arm. About this time he also developed diplopia on lateral gaze (thought in retrospect to have been to the left) and dizzy spells with illusory movement of the environment. These spells occurred while he was flat in bed.

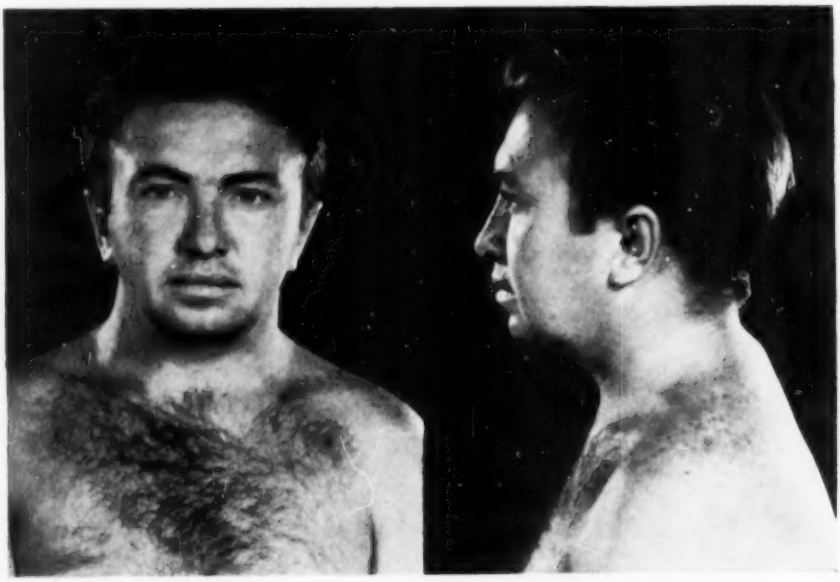

Fig. 5 (Case 4).—Front and side views of patient showing "bull neck," with an abnormally short distance between the occiput and the vertebra prominens (seventh cervical vertebra).

On admission to the Army hospital his outstanding signs and symptoms were left-sided weakness, hypalgesia on the left side of the neck, and nystagmus. A tentative diagnosis of multiple sclerosis was made. X-rays of the skull, however, showed the typical appearance of platybasia with invagination of the base of the skull and occipitalization of the atlas. The patient was then transferred to the Massachusetts General Hospital.

On admission to the latter hospital, the patient, who was 27 years of age, showed the following neurologic and ocular abnormalities: The pupils were unequal, the right being 6 mm. and the left 3 mm. in diameter. There was a horizontal nystagmus to either side, but more marked to the left. Corneal reflexes were sluggish. The muscle strength was diminished on the left, and more in the legs than in the arms. There was slight adiadokokinesis on the left, and the heel-to-shin test was performed less well on the left. There was sustained left ankle and patellar clonus with an extensor plantar reflex on the left. Hypalgesia was present on the left, corresponding to the fourth cervical to the first thoracic dermatomes. The patient's neck was conspicuously short, and the hair line extended to the base of his neck (Fig. 5).

X-rays of the skull showed a deformity consisting of marked protrusion of the base into the cerebral fossa around the foramen, leading to a short posterior fossa (Fig. 6). The first and practically the entire second cervical vertebra lay above a plane connecting the posterior edge of the foramen magnum with the hard palate. The foramen magnum was of practically normal size. The findings were thought to be typical of platybasia.

A lumbar puncture revealed clear spinal fluid with a total protein of .38 mg. per 100 cc. and a pressure of 130 mm. of water. Wassermann tests on the spinal fluid and blood serum were normal.

An occipital decompression and upper cervical laminectomy were done. The dura was not opened.

The immediate postoperative course was uneventful except for two or three seizures characterized by the arms and legs becoming numb and by a generalized shaking. The patient's preoperative symptoms continued, with possible slight worsening for a time.

Ten years after the operation the patient, then age 37, was recalled for survey. His chief symptoms were as follows: In the visual sphere, he felt that his eyes were weak; particularly, he was unable to coordinate his eye movements with those of his head, so that he overshot the

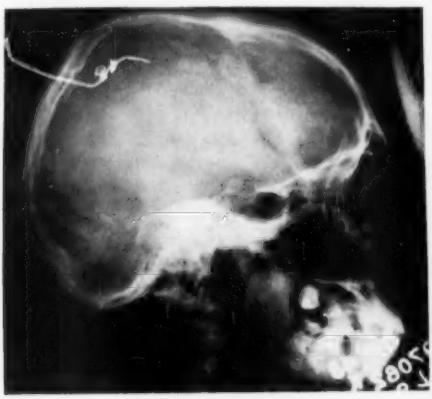

Fig. 6 (Case 4).—Lateral view of the skull, showing severe platybasia with invagination of the occipital bone into the posterior fossa.

point of fixation on movement of his head. The patient also stated that he had a sensation of bones crunching on turning his head. Headaches and nausea occurred on exertion or on his attempting to lift some heavy object; these headaches were chiefly occipital. There was persistent weakness of the left hand and leg and unsteadiness in walking. A new symptom which had occurred during the previous year was increasing impotence. He had had no difficulty in swallowing but had had some slurring of speech when excited. There had been no further change in gait.

Examination of his eyes at this time showed a vertical nystagmus in the primary position of gaze, with the fast component downward. This increased on downward gaze and decreased on upward gaze. There was a superimposed horizontal nystagmus on looking to either side, with a fast component toward the side of gaze. This was more marked on gaze to the right than to the left. There was a consistent overshoot (dysmetria) on looking from the right to the midline or to the left, but accurate fixation on looking from the left to the midline or to the right. During the act of reading the vertical nystagmus was inhibited and the patient read a line from left to right with normal facility, but on returning to the first part of the next line he overshot the mark and, in consequence, hesitated in his reading. The patient himself was not aware of this. Finally, there was a horizontal diplopia present on extreme lateral gaze to the left compatible with weakness of the left external rectus muscle.

Neurologic examination showed that the speech was slightly slurred. The tongue showed fasciculations with atrophy of the right side and some fasciculations of the left side. There was some hypalgesia in the second cervical segment on the left. Movements of the neck were limited in all directions. No crepitus was felt, although the patient was aware of a crunching sensation. There was an extensor plantar reflex on the left and spasticity of the left leg with increased reflexes on the left.

Repeat x-rays showed, aside from the operative defect, an extension of the odontoid process approximately 2 cm. above the line connecting the foramen magnum and the hard palate.

This patient had severe headaches in childhood and adolescence which may or may not have been related to his cervical-skull anomaly. At the age of 17, however, he developed progressive symptoms pointing to involvement of the pyramidal tract, spinothalamic tract, and cerebellum or cerebellar pathways, with nystagmus and diplopia. The diagnosis of multiple sclerosis was suggested, but the insidious onset and steady course without remissions were against this. The definitive diagnosis of platybasia was made by x-rays. A decompressive operation was done, with little obvious change in the symptoms. An Arnold-Chiari deformity was thought to be present, but since the dura mater was not opened it could not be confirmed.

CASE 5.—*Platybasia with apparently rapid onset of symptoms of ataxia, pyramidal tract signs, and nystagmus at the age of 30. Clinical diagnosis of multiple sclerosis.*

C. C. (812870), a 30-year-old woman, who has been under observation for three months. She denied having had any significant symptoms until one month prior to her first visit, when, associated with an attack of tonsillitis, she noted headache, weakness, and dizziness. She was referred to the hospital by her local physician, who had noted nystagmus, hyperreflexia, ankle clonus, and ataxia and had accordingly made the diagnosis of multiple sclerosis.

She had noted that she had to walk with a wide base and was unable to maintain her balance on a straight line. Although she had no visual complaint, she did say she had pain in the back of her neck when she looked upward. This pain in her neck was described as a crick and was helped by lying down. On the negative side, she denied having difficulty with swallowing, clumsiness, or numbness.

Examination of the eyes showed as most conspicuous a vertical nystagmus present in the primary position of gaze and increasing on looking upward. This was somewhat less with the head hyperextended than with the head erect. A horizontal nystagmus occurred on gaze to either side, and in consequence the patient had assumed a habit of moving her head instead of her eyes on looking about. The pupils were of normal size and reaction. The fundi were normal.

On neurologic examination the patient showed an unsteadiness of gait and awkwardness in the heel-to-shin test that was most marked on the left. There was a generalized hyperreflexia and a bilateral extensor plantar response. There was no sensory disturbance.

General physical examination showed a short neck as the only significant abnormality.

A lumbar puncture revealed clear spinal fluid under normal pressure and having a total protein of 66 mg. per 100 cc.

X-rays of the skull showed severe basilar invagination of the skull with the tip of the odontoid 1.5 cm. above Chamberlain's line (Fig. 7). A laminogram of the cervical vertebra showed fusion of the occipital bone to the atlas (Fig. 8).

The patient is not particularly incapacitated by her neurologic symptoms at present, and, accordingly, surgery is not planned for the immediate future.

The apparently rapid onset of symptoms certainly justified the initial impression of multiple sclerosis. The absence of sensory findings, however, and the limitation of the signs to the brain stem region suggested platybasia. The definitive diagnosis was again made by x-rays.

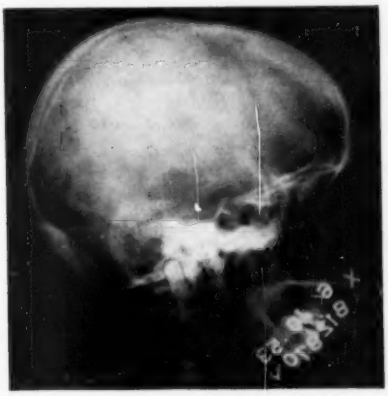

Fig. 7 (Case 5).—Lateral view of the base of the skull showing the upward extension of the odontoid process. A fusion of the atlas to the occiput which was present in this patient is not well shown in this view.

Fig. 8 (Case 5).—Anteroposterior laminogram of the cervical vertebrae showing the points of fusion of the occipital bone with the atlas (courtesy of Dr. Joseph Hanelin).

CASE 6.—*Platybasia, with chief symptoms of headache, an unusual type of vertical nystagmus, and unsteadiness of gait, all of many years' duration. Diagnosis long overlooked.*

J. S. (562082), a 43-year-old man, whose chief complaints consisted of occipital headaches, blurring of vision, and unsteadiness of gait of many years' duration. At the age of 25 he was admitted to a hospital with the foregoing complaints, which were then said to have been present for nine years; they were thought to have followed a minor operation on the nose.

On examination at the age of 25 the patient was noted to have a vertical nystagmus with the fast component directed downward, some diminution of sensation in the right side of the face and right cornea, a wide-based gait, with falling to the left, and a left ankle clonus. Routine skull x-rays were reported as showing nothing abnormal. The patient also had otorrhea on the right of many years' duration, and a right radical mastoidectomy was done.

At the age of 37 the patient was studied at the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary. In the meantime the complaints of headache, blurred vision, and unsteadiness had continued and were more recently accompanied by diplopia, by an

Fig. 9 (Case 6).—Lateral view of skull retouched to show crown of odontoid process well above Chamberlain's line. This x-ray was taken after myelography and shows iodized oil (Lipiodol) in the spinal canal and the basal cistern. Other x-rays of this patient showed the bifid first cervical vertebra, the unusually large foramen magnum, and occipitalization of the atlas.

ache that spread down the back of the neck, and by transient spells of dizziness. The headache was said to be accentuated by movements of the head and neck.

Examination at the age of 37 showed a vertical nystagmus on looking to either side and to some extent on looking upward, but the fast component was always directed downward; no nystagmus was present on looking down, and in this position the patient had least blurring. A left hypertropia was present, simulating a left inferior rectus paresis. The patient was unable to walk a straight line; the knee and ankle reflexes were hyperactive; a bilateral ankle clonus was elicited, but the plantar reflexes were flexor. A lumbar puncture revealed no abnormality, and the spinal fluid protein was 46 mg. per 100 cc. Routine skull x-rays were again reported as negative.

In the six years that the patient had been followed since the foregoing note was made, there was slight worsening of his symptoms, and, in addition, a bilateral loss of sensation in the area of the third dermatome, a loss of position sense in the toes, and the development of a duodenal ulcer. The nystagmus continued to be predominantly vertical, and accentuated on upward gaze, with the fast component directed downward!

An x-ray taken at this time for the specific possibility of an abnormality in the region of the foramen magnum revealed a bifid first cervical vertebra, a large foramen magnum, occipitalization of the atlas, and extension of the odontoid process above Chamberlain's line. The findings were interpreted as showing a marked degree of platybasia. Cervical myelography showed no defect in filling.

The symptoms in this patient began at about 18 years of age. When he was first studied, at 25 years of age, the noteworthy findings were headache, vertical nystagmus, and unsteadiness of gait. There was some worsening but remarkably little qualitative change during the subsequent 18 years of observation, and no real remissions. An extraordinary feature was the fact that the vertical nystagmus had a fast component directed downward, even though the nystagmus was accentuated by upward gaze and disappeared on downward gaze.

Perhaps the most instructive feature of this case, and of several other cases in this series, was the fact that routine skull x-rays taken over the years gave no suggestion of the anomaly. Thus, various diagnoses had long been weighed, including multiple sclerosis, brain stem tumor, brain abscess, vascular accident, and congenital defect in the brain stem. Only when x-rays were taken specifically for visualization of the foramen magnum region was the true diagnosis apparent. This underscores the clinician's responsibility in suspecting the entity on clinical grounds and requesting specific x-ray views.

CASE 7.—*Presumed Arnold-Chiari malformation occurring in a patient with meningomyelocele, spina bifida, and mild hydrocephalus. The eyes showed vertical and horizontal nystagmus of the jerk type.*

A. H. (668584), a 14-year-old girl, whose chief complaint was a disturbance of gait dating back to infancy. She had had a meningomyelocele, which was operated upon at the age of 6 weeks. Subsequently, she was noted to have a hydrocephalus and an equinus deformity. She began to walk at the age of 4 and has always been described as being stiff-legged and to have a rolling of the pelvis. Mental development has been thought to be normal. It was noteworthy, however, that she developed control of her urinary bladder only at 8 years of age.

Examination, aside from that of the eyes, showed the following picture: There was a mild degree of macrocephaly. The gait appeared spastic, with a characteristic scissors movement; and the reflexes were hyperactive, but the plantar reflexes were flexor and there was no ankle clonus. Adiadokokinesis was not demonstrable, and sensation was normal.

The noteworthy finding in the eyes was the jerk nystagmus: vertical nystagmus in the primary position of gaze, increasing on looking upward (absent on downward gaze), and a horizontal nystagmus on deviation of the eyes more than 20 degrees to either side, with the fast component always in the direction of gaze. The patient also had a high hyperopia (+5.00 D.) and an exotropia when she wore her correction. There was, however, no limitation of eye movements and no skew deviation. The slight reduction in visual acuity to 20/40 was thought to be compatible with the hyperopia.

X-ray films of the skull showed a brachiocephalic type of cranial vault but no abnormality in the foramen magnum region. The lumbosacral region showed a wide-open spina bifida of the lower two lumbar segments of the sacrum. Further investigation was not thought warranted.

Without myelographic or anatomic confirmation the diagnosis of an Arnold-Chiari malformation must be tentative only. However, the occurrence of the vertical and horizontal nystagmus was in itself indicative of a posterior fossa lesion, and the rest of the neurologic signs were compatible with this. The coexistence of hydrocephalus, meningomyelocele, and spina bifida is characteristic of the type of Arnold-Chiari deformtiy that is found in infancy.

CASE 8.—*Platybasia and Arnold-Chiari malformation in a 16-year-old boy with progressive unsteadiness of gait of five years' duration. Bilateral occipital headaches, vertigo, and diplopia, provoked by sneezing; vertical and horizontal nystagmus, varying with head posture; flutter-like oscillations of the eyes, and ocular motor dysmetria. Occipital craniectomy and removal of the laminae of the first and second vertebrae.*

C. H. (480205). The protocol of this case is to be found in the ARCHIVES, where it was included as "Case B 4," illustrating the flutter phenomenon.[23] The routine skull x-rays of this patient were reported as showing nothing abnormal. Further lateral skull films, however, showed the odontoid process and anterior mass of the atlas partly above Chamberlain's line, making a definite diagnosis of platybasia (Fig. 10).

The nystagmus in this patient was vertical and horizontal, as noted in all the previous cases, but its variation with position of the head, similar to that in Case 1, is especially noteworthy. The flutter phenomenon and ocular motor dysmetria have been interpreted as indicating involvement of the cerebellum or cerebellar pathways.[23]

Fig. 10 (Case 8).—Lateral view of skull showing platybasia.

CASE 9.—*Probable platybasia with involvement of the lower medulla, causing hemiplegia, crossed hemianesthesia, autonomic dysfunction, scoliosis, and vertical and horizontal nystagmus.*

M. M. (534151), a 28-year-old clerk, who was first seen at the Massachusetts General Hospital at the age of 25 for the complaint of spontaneous seminal emissions occurring whenever his right foot became cold.

At the age of 4 years the patient had had convulsions over a period of several months, and after this he developed progressive scoliosis, weakness and deformity of the left arm and leg, and hyperhidrosis of the right side.

Neurologic examination showed, in addition to the scoliosis, hyperreflexic hemiparesis on the left, atrophy of the left extremities, sympathetic paralysis on the left (including Horner's syndrome), hypesthesia on the right side of the body, and bilateral plantar extensor response. The eyes showed in the primary direction of gaze a vertical nystagmus, which became accentuated on looking either upward or downward, and a horizontal nystagmus on looking to either side, with the fast component always in the direction of gaze. There was no dissociation of the eyes, and the opticokinetic response was normal. His only visual complaint was inability to follow a rapidly moving object, such as a baseball or an automobile.

By roentgenography, the posterior fossa of the skull appeared to be unusually small, and the odontoid extended upward to an abnormal extent. The x-ray findings were interpreted as consistent with a mild degree of platybasia; yet myelography showed no block in the upper cervical spine.

A right lumbar sympathectomy alleviated his chief complaint of spontaneous seminal emission, and later a right thoracic sympathectomy was done to cure his hyperhidrosis. The patient has been followed for three years since he was first seen and has shown no definite change in his ocular findings.

The vertical and horizontal nystagmus in this case, together with the neurologic signs, indicated a lesion of the posterior fossa, and the x-ray suggested platybasia. That the bony abnormality of the skull was responsible for the neurologic defect must remain undecided, especially since myelography showed no block; but it is noteworthy that at least one case of the Arnold-Chiari deformity has previously been reported in association with profound scoliosis, such as this patient had.[21]

COMMENT

Of the ocular signs and symptoms, the one which all the cases have in common is a vertical and horizontal nystagmus of the jerk type. While horizontal nystagmus is not an uncommon occurrence with lesions in many parts of the central nervous system (and may even be "congenital"), vertical nystagmus indicates, with rare exceptions, a lesion of the posterior fossa. However, the type of nystagmus offers no clue as to the type of the lesion. Its variation with head posture may be significant; at least, it was present in three of the patients in this series to a greater degree than we have seen in other conditions. But this postural variation cannot be considered pathognomonic, since Nylén [24] has noted it with tumors of the cerebellum and brain stem. Skew deviation was found in three patients, and an unexplained horizontal diplopia was found in three patients.

The differentiation of platybasia and the Arnold-Chiari malformation from other lesions of the posterior fossa cannot be made with certainty on the basis of the clinical signs and symptoms alone. The diagnosis may be suspected, however, when the foregoing ocular signs come on insidiously during adolescence, along with other evidence of brain stem and cerebellar involvement, especially when they are accompanied by pain in the neck and are provoked by coughing or sneezing,‖ or by change in head position. A reasonably definite diagnosis may be made by skull roentgenography in the case of platybasia, and often by myelography in the case of the Arnold-Chiari malformation. However, accurate measurements of the odontoid process can be made only with a true lateral projection of the skull, including the upper three cervical vertebrae. It should be emphasized that the presence of platybasia may be easily overlooked in routine skull films, as was true in four of the present cases, unless the anomaly is purposefully looked for. Thus the responsibility for suspecting it rests on the clinician. It is also evident from Cases 3, 6, and 9 of the present series that myelography is not always indicative of the compression of the brain stem.

‖ While the sneezing would be inferred to be only incidental to the deformity, it is noteworthy that sneezing was one of the presenting complaints in another patient (362078) with the Arnold-Chiari malformation and was completely relieved by suboccipital decompression. It is also worth mentioning that this patient, who is not included in the present series for lack of an adequate ophthalmological work-up, had an exacerbation of his ataxia, headache, and blurred vision after a sneezing spell and was relieved by forceful rubbing of the back of his neck.

SUMMARY AND CONCLUSIONS

The entities commonly known as platybasia and the Arnold-Chiari malformation have prominent ophthalmological signs and symptoms, which may be confused with those of multiple sclerosis and brain stem tumor; yet they have not received widespread recognition in the ophthalmological literature.

The ophthalmological signs, consisting of horizontal and vertical nystagmus and skew deviation, are such as one finds with any lesion of the posterior fossa, but the course, and especially the acute exacerbation, with coughing and sneezing and on the assumption of certain head positions, are suggestive of either of the anomalies.

Nine case reports are presented: three in which the diagnosis of platybasia and the Arnold-Chiari malformation was proved by anatomic study; one in which the diagnosis of platybasia alone was similarly substantiated; four in which the diagnosis of platybasia was made by x-ray, and one in which the diagnosis of the Arnold-Chiari malformation was assumed on the basis of the signs and symptoms.

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ELECTRORETINOGRAM IN CIRCULATORY DISTURBANCES OF THE RETINA

IV. Electroretinogram in Cases of Retinal and Choroidal Hypertension and Arteriosclerosis

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IN HIS MONOGRAPH Karpe [1] has indicated a possible alteration in the electroretinographic response in cases of hypertensive retinopathy. In one case, showing narrowing of the arteries with retinal exudates, he found a subnormal response, whereas in another, showing slight hypertensive vascular alterations, the ERG recorded was normal. The same results have been reported by Euzière, Passouant, and Cazaban,[2] who found a normal ERG in retinal sclerosis, but a pathologic ERG in more advanced stages. Regarding the ERG as a prognostic sign in cases of hypertensive retinopathy, these authors say:

Mais nous ne serions pas étonnés si ce mode d'examen permettait d'apporter un nouvel élément de prognostic dans le rétinopathie hypertensive.

Dollfus and Chavignac [3] studied nine cases of hypertensive retinopathy. They state:

On est frappé de constater que l'ERG de ces malades ne présente pas d'altérations graves et qu'au contraire l'onde b est presque toujours d'une amplitude maximale ou supramaximale.

In several previous papers I have discussed also the influence of hypertensive and/or arteriosclerotic alterations in the retina and choroid.*

The present investigation deals with the electroretinographic records in a number of cases showing vascular retinal and choroidal alterations caused by hypertension and arteriosclerosis. I investigated the following groups of retinal vascular involvement:

1. Hypertensive retinopathy without arteriosclerosis (11 cases)
2. Hypertensive retinopathy with arteriosclerosis (50 cases)
3. Diffuse atherosclerosis of the retina without hypertension (28 cases)
4. Diffuse atherosclerosis of the choroid with and without hypertension (19 cases)

The present study has been partly covered by one or more of the previous papers on electroretinography in circulatory disturbances of the retina,† as hypertensive alterations and vascular sclerosis in the retina and choroid play a most important role in the development of the pathological conditions already discussed (occlusion of central and retinal veins and arteries; senile macular degeneration).

MATERIAL

In each of the groups investigated cases showing minor vascular involvement have been compared. The distribution of the material over the various age groups is shown in Figure 1.

* References 4 through 6.
† References 7 through 9.

All patients showing hypertensive retinopathy without arteriosclerosis (Group 1) are under 50 years of age. The material in Groups 2 and 3 consists entirely of patients above the age of 50. These two groups can be compared as a whole, as they show identical signs of vascular involvement. As minor signs I have taken tortuosity and irregularity of the vascular lumen, arteriovenous crossings, "copper-wire" arteries, and sheathing of the vessels. Most, if not all, cases in Groups I and II of the Wagener-Keith classification belong to this group of minor involvement. In Group 1 (hypertensive retinopathy without arteriosclerosis) a general attenuation of the arteries is considered to be a minor sign of vascular involvement.

Malignant signs (in malignant hypertensive or arteriosclerotic retinopathy) are marked hemorrhages, exudates, and edema of the retina and optic disc (Group 2). Groups III and IV of the Wagener-Keith classification are incorporated in this

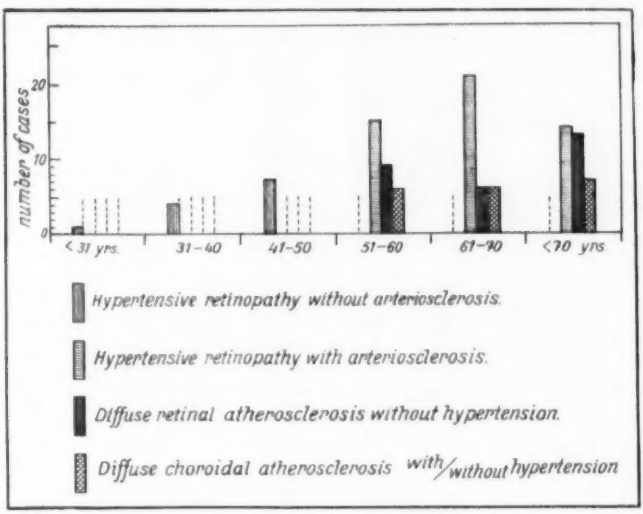

Fig. 1.—Distribution over the different age groups of 108 cases showing chorioretinal vascular involvement.

group. It is, of course, not always possible to make a clear distinction between these two groups of mild and malignant retinal involvement.

The blood pressure of the patients in Groups 1 and 2, even after a period of 30 minutes' rest, showed diastolic values of 100 mm. Hg or more. The nonhypertensive patients (Groups 3 and 4) showed a blood pressure of not more than 150/90, at least after the 30-minute period of rest.

Several cases of doubtful hypertension have been eliminated from the material. Cases showing retinal complications (angiospasm, aneurysm, thrombosis, or macular involvement) are not incorporated in the present material.

TECHNIQUE

The recording technique was in most cases the same as that described in previous articles. However, part of the investigation was carried out with a two-channel amplifier ‡ used for the recording of the electroretinogram of the two eyes at the same time.

‡ This instrument was supplied in part by the Netherlands Health Organisation T.N.O.

As I described before, an increase in the b-potential of the ERG following a prolonged period of rest in the dark can be demonstrated in several cases of vascular involvement. The dark-adapting period of five minutes, generally accepted as sufficient in clinical electroretinography, has been extended in the cases discussed in the present investigation to 30 minutes. In this article I shall discuss at some length the results obtained in the records taken over this prolonged period of rest and dark adaptation.

RESULTS

1. *Hypertensive Retinopathy Without Arteriosclerosis.*—Eleven patients were examined, all under the age of 50. Of the seven patients showing signs of minor

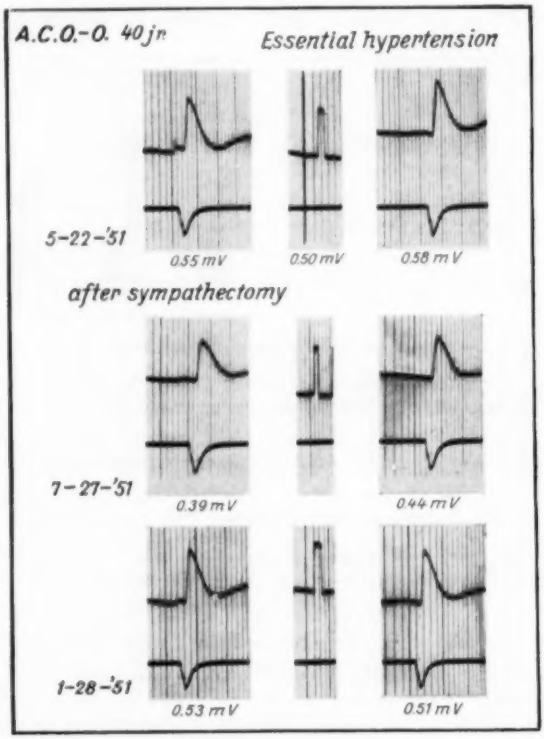

Fig. 2.—ERG's in a case of hypertensive retinopathy without arteriosclerosis before and after bilateral sympathectomy; temporary normalization of the supernormal electrical responses following operation.

involvement of the retina, only two showed a normal ERG, whereas in five a supernormal response could be recorded. After a prolonged stay in the darkroom there was no alteration in the electrical response. I took as normal a response with a b-potential of between 0.25 and 0.45 mv. Values up to 0.60 mv were recorded in this group. In three of the seven patients in this group a negative + ERG, showing a marked a-wave, was met with.

A discussion of the ERG's recorded on one of the patients belonging to the group showing only minor signs of retinal involvement seems to be of interest.

A. O., a woman aged 40, suffering from essential hypertension, showed, apart from signs of mild hypertensive retinopathy, quite normal visual acuity. The ERG recorded showed a supernormal response (Fig. 2). Bilateral sympathectomy was followed by a normalization of the blood pressure. The fundus picture, however, was unaltered, although the ERG became normal. Several months later the blood pressure rose again, as did the b-potential of the ERG, again showing a supernormal response. The patient's complaints, however, had disappeared after the operations and did not return. The fundus picture did not show the least alteration during the period in which the ERG altered considerably.

I consider the supernormal b-potential before sympathectomy as due to a raised irritability of the neurons of the second order, from which it is believed that the b-wave originates. This raised irritability could be explained, in my opinion, by an insufficient oxygen supply following the constriction of the retinal vessels which

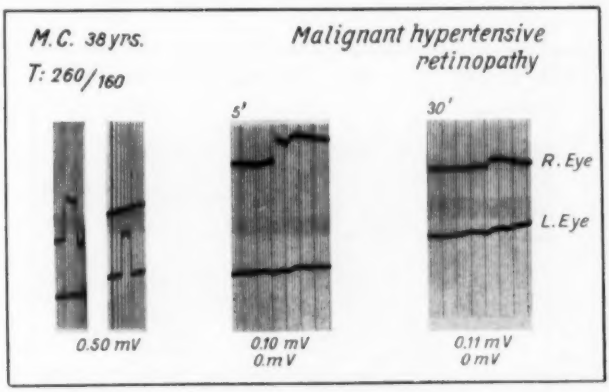

Fig. 3.—ERG in a case of malignant hypertensive retinopathy two days before death.

is found regularly in this condition. After sympathectomy this spastic condition disappeared, and, in consequence, the retinal metabolism (oxygen supply) returned to normal and a normal ERG could be recorded.

When, at a later date, the condition worsened again and the blood pressure rose, the retinal metabolism deteriorated and the electrical response changed back into a supernormal ERG. However, the ophthalmoscope did not show any definite change during this period.

Of the four patients showing signs of malignant hypertensive retinopathy, two showed a supernormal ERG with a b-potential of well over 0.60 mv, one a normal, and one a subnormal response. Of the following patients a discussion is of interest.

B. B., a man aged 28, suffered from hypertension due to a pheochromocytoma. The ophthalmoscope revealed a hypertensive retinopathy of the malignant type. The visual acuity was normal. The ERG of both eyes showed normal values. After operation the blood pressure fell abruptly from 175/120 to 130/70. The fundus picture changed toward the normal state; the ERG remained normal throughout. In my opinion, in spite of the increased blood pressure, the metabolism of the retina as a whole must have been fairly normal, with a sufficient oxygen supply reaching the retinal neurones.

M. C., a woman aged 38, was suffering from malignant hypertensive retinopathy, with a blood pressure of 260/160. The right retina gave a subnormal response, whereas the ERG of the left eye was extinguished (Fig. 3).

In my opinion, such a pathological response can be explained only as an expression of a highly altered metabolism of the retina, though neither the visual acuity nor the visual fields showed marked alterations. Bearing in mind this electroretinographic response, I was not surprised that this patient died suddenly two days after the recording of the ERG.

2. Hypertensive Retinopathy with Arteriosclerosis.—I examined electroretinographically 50 patients showing hypertensive retinopathy with signs of a general and/or retinal arteriosclerosis. All patients were over 50 years of age (Fig. 1).

Thirty-five patients were examined over a longer period of rest and dark adaptation; the importance of such a prolonged rest has already been stressed.[9] Of these, 32 patients showed signs of minor involvement of the retina, whereas only 3 showed the picture of a malignant hypertensive retinopathy with marked exudates, hemorrhages, and edema of the optic discs and surrounding retinas. Electroretinography,

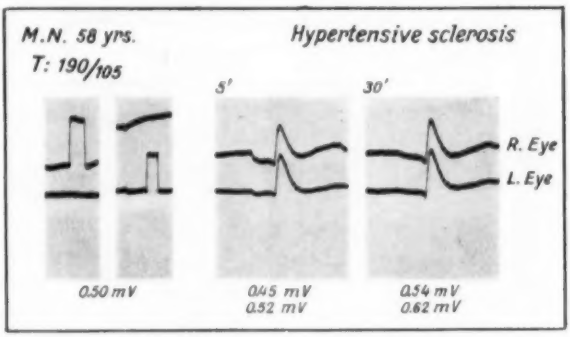

Fig. 4.—ERG in a case of hypertensive sclerosis showing minor signs of vascular involvement. The supernormal response points to a definite impairment of the retinal metabolism.

performed after the usual period of five minutes' rest in the dark, revealed in the group with minor retinal involvement the following distribution: a subnormal response in one or both eyes, 8 cases; a normal response in both eyes, 21 cases, and a supernormal response in one or both eyes, 3 cases. The limits of a "normal" b-potential have been chosen arbitrarily as between 0.25 and 0.45 mv.

After a prolonged period of rest in the dark, up to 30 minutes, all subnormal ERG'S turned into normal ones, whereas 7 normal responses changed into supernormal responses. In six cases a marked a-wave could be recorded, by definition: A negative ERG was found.

The improvement in height of the b-potential, following the prolonged rest period, indicates in my opinion that, owing to this rest, the metabolic condition of the retina was improved. From an electroretinographic viewpoint, some of the cases belonging to this group are of importance.

M. N., a man aged 58. Blood pressure 190/105, showed some irregularity in the caliber of the retinal vessels and a slight pallor of the optic disc of the left eye. The macular area was nearly normal. Visual acuity: 10/10 and 7/10. The ERG was normal for the right eye and super-

normal for the left eye, changing after a period of 30 minutes' rest in the dark to a supernormal b-potential in both eyes with a marked a-wave: A negative +ERG was recorded (Fig. 4). In my opinion, this supernormal electrical response points to a definite, though not very serious, impairment of the retinal metabolism.

In the group of the severer cases of hypertensive sclerosis of the retina, varying responses have been met with, indicating the various conditions under which the retinas of these patients are functioning. The worse the condition of the retina (oxygenation of the retinal cells), the lower the b-potential will be.

A. L., a man aged 66, presented a fairly normal visual acuity with the fundus picture of malignant hypertensive retinopathy. Blood pressure 210/105. The ERG was extinguished for the right eye and subnormal for the left eye (Fig. 5). After a 30-minute period of rest, both retinas gave a normal response. I am convinced that, owing to the prolonged rest in the dark, the metabolic condition was changed considerably. However, it is by no means certain that this "normal" b-potential, recorded after 30 minutes, means that the metabolism (especially the oxygen supply) was normal again. The possibility remains that this so-called "normal" response

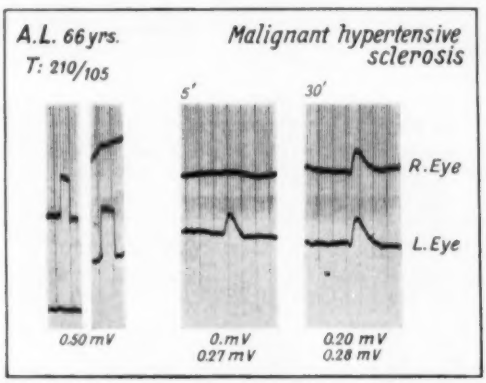

Fig. 5.—Malignant hypertensive retinopathy. Electroretinographic responses change as a result of prolonged rest, pointing to an amelioration of the retinal metabolism.

was a decreased supernormal one, which, however, could no longer be attained, owing to the fixed condition of the retinal changes (definite loss of retinal cells, for instance).

3. *Diffuse Retinal Atherosclerosis Without Hypertension.*—Twenty-eight cases were examined, of which 23 were studied also after a prolonged period of rest and dark adaptation. The distribution over the various age groups can be learned from Figure 1. This distribution is more or less the same in the group of hypertensive retinopathy with arteriosclerosis (Group 2) and in the group now under discussion.

Electroretinography revealed, after the usual period of five minutes' rest in the dark, in this group, showing only minor signs of retinal involvement, a subnormal response in one or both eyes, in 5 cases; a normal response in both eyes, in 16 cases, and a supernormal response in one or both eyes, in 2 cases.

Here, also, I have chosen the limits of a "normal" b-potential arbitrarily as between 0.25 and 0.45 mv, as was done in Group 2. A prolonged rest in the dark changed the ERG type in several cases, though in less than in the previous group,

that of hypertensive retinopathy with arteriosclerosis. Two subnormal ERG's turned into normal ones; eight normal responses turned into supernormal ones. In four patients a negative ERG could be recorded.

The results obtained in the electroretinographic study of the patients belonging to this group justify a further discussion in the following case histories:

J. L., a woman aged 70. Blood presure 150/80. This patient showed in her fundus signs of only very slight involvement of the retinal vessels. There was some pigment degeneration in the periphery of the retina. Visual acuity normal. Macular region: no pathological changes. The

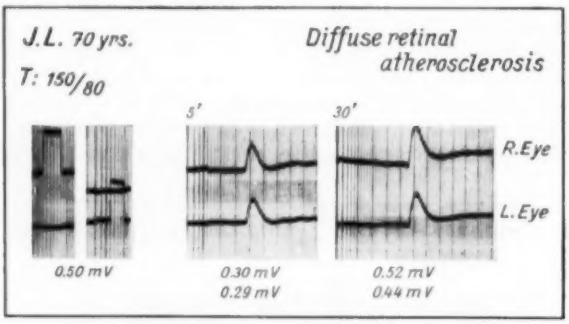

Fig. 6.—ERG in a case of diffuse retinal atherosclerosis without hypertension. Changing of ERG type following a 30-minute period of rest in the darkroom.

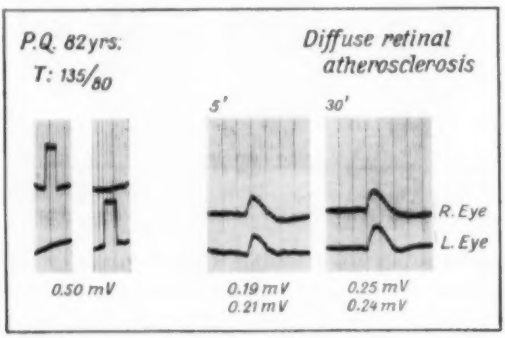

Fig. 7.—An insignificant improvement in height of the b-wave of the ERG in a patient suffering from a diffuse atherosclerosis of the retina without hypertension.

ERG showed "normal" values, changing after a period of prolonged rest in the darkroom, to supernormal values of the b-potentials (Fig 6).

In my opinion, the retinas had retained the capacity to improve the nutrition of the retinal neurones, so that the electrical response could improve too. In other instances this was not the case, as is shown by the following case:

P. Q., a man aged 82. Blood pressure 135/80. Only slight alterations in fundus. Visual acuity only slightly impaired by senile alterations in the lens.

The ERG, recorded after the usual five minutes of dark adaptation and rest, was of the subnormal type (b-potentials 0.19 and 0.21 mv, respectively). After a 30-minute period of rest in the darkroom, the b-potentials showed values of 0.25 and 0.24 mv (Fig. 7).

According to Karpe,[10] the normal value of the b-potential above the age of 50 decreases as part of the process of aging, so that the mean value between the ages of 70 and 74 is 0.23 mv. This value, however, was based on only three subjects. As I made clear in a previous article,[9] it is questionable whether this value is really the normal height of the b-potential at this age. From my own material, I am inclined to believe that there is no significant decrease in b-potential with age, at least if there is no sign of an arteriosclerotic process. However, as the process of general arteriosclerosis above the age of 60 is a very common finding, there will be in many cases, even when no signs of arteriosclerosis are demonstrable with the ophthalmoscope, an alteration of the ERG, with, as a consequence, the possibility of the recording of a subnormal response.

4. *Diffuse Atherosclerosis of the Choroid With and Without Hypertension.*—Nineteen cases were studied, of which 15 showed only minor involvement of the choriocapillary layer, whereas in 4 cases the choroidal sclerosis was considerable.

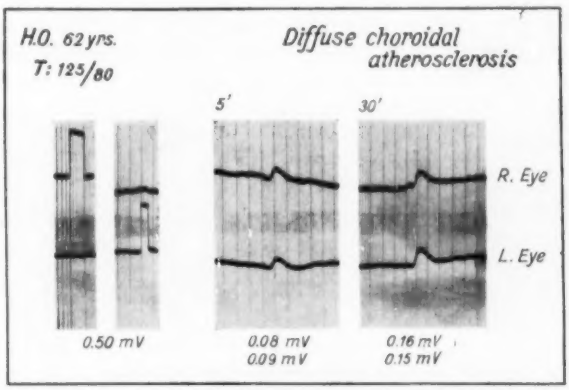

Fig. 8.—ERG in a case showing a diffuse atherosclerosis of the choriocapillary layers. Some improvement in b-potential following a 30-minute rest, as a result of improved metabolic condition.

In only two cases was an arterial hypertension observed. As the lesion of the choriocapillary layer was localized mainly in the posterior pole, it is rather difficult to make any sharp division between cases of senile chorioretinal degeneration (Haab), discussed previously,[9] and cases belonging to the group now under discussion. From the present material I eliminated, however, those cases showing a marked degeneration of the macular area. Diffuse processes localized in the posterior pole have been incorporated in the present material.

After the usual five minutes' rest in the darkroom, I could record in the group of mild choroidal affections a subnormal response in one or both eyes, in 10 cases, and a normal response in both eyes, in 5 cases. A supernormal response could not be recorded in any case. The limits of a "normal" b-potential were chosen, again, as 0.25 and 0.45 mv.

After 30 minutes' rest in the darkroom two subnormal responses had changed into normal ones. In no case was a change from a normal into a supernormal b-potential observed.

As compared with the aforementioned groups of retinal atherosclerosis with and without hypertension, the emphasis lies on the high incidence of a subnormal response, which is even greater if one considers the cases showing a severer sclerosis of the choroidal vessels. All four of these cases responded with a subnormal ERG, which, after a continued rest in the darkroom, changed into a normal response only in one case.

The following cases deserve discussion in more detail.

H. O., a man aged 62. Visual acuity 10/10. In the periphery of the fundus slight sclerotic changes were visible. A narrowing of the visual fields was demonstrable. The macular area showed no abnormalities. Blood pressure 125/80. The ERG of both eyes was of the subnormal type, with b-potentials of 0.08 and 0.09 mv, respectively. After prolonged rest in the darkroom the b-potentials gained some height, reaching 0.16 and 0.15 mv, for the eyes, respectively (Fig. 8).

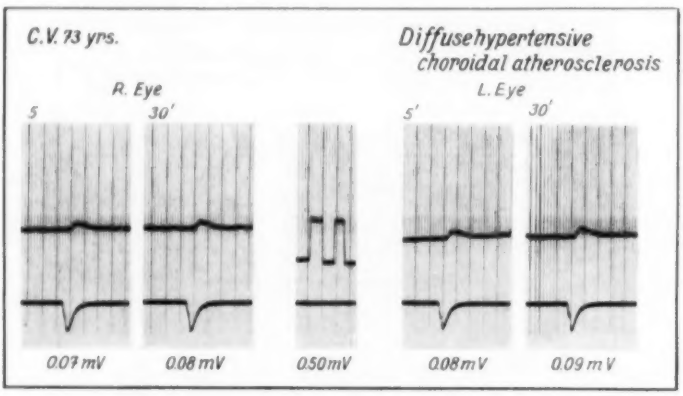

Fig. 9.—ERG in a case showing marked sclerosis of the choriocapillaris; no improvement in electrical response following a prolonged period of rest.

In this case we have to accept the influence of the malnutrition of the photoreceptors, due to the sclerosis of the choriocapillaris. Owing to this fact, it is clear that the response of the neurones of the second order will be also insufficient. As I pointed out previously, the extension of such a sclerotic process can be revealed in vivo only by electroretinography, since in most cases the ophthalmoscopic picture will show only minor pathological alterations.

C. V., a man aged 72. The ophthalmoscope revealed a marked sclerosis of the choriocapillary layers of the posterior pole of both eyes. Vision in the right eye, 4/10; that of the left eye, counting fingers at 3 meters. In the periphery a pigmentary degeneration was visible. The retinal vessels were narrow; a slight pallor of the optic discs completed the picture of a secondary tapetoretinal degeneration based on general arteriosclerosis with hypertension.

The ERG was subnormal, with no improvement in b-potential after a prolonged stay in the dark (Fig. 9). No change in electroretinographic responses has been found during an observation time of over two years. In this period, various vasodilators have been used, in an attempt to improve the chorioretinal circulation. The electrical response following general vasodilation has not changed significantly, though subjectively the retinal condition has been improved.

COMMENT

From a comparison of the results obtained in electroretinographic studies of the patients belonging to the various groups of retinal and choroidal vascular involvement, it is clear, in my opinion, that the incidence of large responses (supernormal b-potentials) is highest in the group of patients suffering from a hypertensive retinopathy without arteriosclerosis (Group 1). In Groups 2 and 3 (hypertensive retinopathy with arteriosclerosis and diffuse atherosclerosis without hypertension, respectively) the supernormal responses were almost equally frequent. Subnormal responses, on the other hand, were mainly recorded in the fourth group, that of diffuse atherosclerosis of the choroid.

In the accompanying Table all patients observed after a prolonged stay in the darkroom, and belonging to the four groups discussed above, are assembled and divided according to the type of response.

Though the material is too small to permit definite conclusions, it is clear from these data that there is a definite difference between Groups 2 and 3. These groups are readily comparable, as the distribution of the various age groups is more or less the same and the ophthalmoscopic picture is identical in all cases. The difference in response between the group with hypertensive sclerosis (Group 2) and the group

ERG's of Patients with Hypertensive and Arteriosclerotic Retinopathy

	No. of Cases	Types of ERG Response, in Percentages		
		Subnormal	Normal	Supernormal
Hypertensive retinopathy without arteriosclerosis	7	0	29	71
Hypertensive retinopathy with arteriosclerosis	32	0	69	31
Diffuse retinal atherosclerosis without hypertension	23	13	52	35
Diffuse choroidal atherosclerosis with/without hypertension	15	53	47	0

with diffuse retinal sclerosis without hypertension (Group 3) can be ascribed, in my opinion, only to the absence of increased blood pressure in the latter.

If we consider the values of the b-potentials after the usual rest in the darkroom of five minutes, no difference can be found between the responses in the cases belonging to these two groups, which show 25 and 22% subnormal responses, respectively. Only after a prolonged rest is the difference marked: In the group with hypertension all subnormal responses have vanished, whereas in the group without hypertension the decrease in the number of subnormal responses is only from 22 to 13%.

In my opinion, the hypertension alone is responsible for this result. The insufficient oxygenation of the retinal cells can thus be restored, at least partially, after a prolonged rest. This metabolic improvement finds its expression in an improvement in the b-potential. This finding supports objectively the generally accepted opinion that one must be very careful with antihypertensive therapy in cases of hypertensive sclerosis.

Further electroretinographic work in this field to support the present findings will be published in due course. We are convinced that it has been demonstrated that the hypertension is an essential mechanism of the organism in making possible a more or less sufficient nutrition of the retinal cells.

As I stressed earlier, the supernormal electrical response is, in my opinion, an expression of an increased irritability of the retinal neurones, owing to the fact that the metabolic condition is not fully sufficient. In most cases of hypertensive retinopathy without arteriosclerosis (Group 1) we found a supernormal response. Some cases showed a temporary normalization of the b-potential following temporary normalization of the blood pressure (Fig. 2), as a result of an improvement in the retinal metabolism (resolution of a spastic condition in the retinal vessels).

For evaluation of the retinal condition it is essential, in my opinion, to observe the reaction to the light stimulus after a period of prolonged rest. If a subnormal response turns into a normal one, I consider it as a favorable point in the prognosis of the case. When a normal response turns into a supernormal one after 30 minutes' rest, this indicates that this so-called "normal" response was really not normal, but that we have to consider it as a decreased supernormal response, which showed this decrease only because the metabolic condition was insufficient. When long standing, it can possibly change into a permanent subnormal response, as when, for instance, part of the retinal elements is definitely destroyed. The recording of the ERG over a period of more than five minutes' rest and dark adaptation, up to at least 30 minutes, must thus be considered as essential in ocular circulatory disturbances.

SUMMARY

Electroretinography has been applied in 108 cases showing vascular retinal and choroidal involvement. Four groups have been investigated: (1) hypertensive retinopathy without arteriosclerosis; (2) hypertensive retinopathy with arteriosclerosis; (3) diffuse retinal atherosclerosis without hypertension, and (4) diffuse choroidal atherosclerosis with/without hypertension.

In patients showing minor signs of vascular involvement and belonging to Group 1, the ERG recorded is predominantly a supernormal one, as a result of an insufficient metabolic condition of the retinal neurones, owing to a constriction of the retinal vessels. In one case bilateral sympathectomy resulted in a normalization of the electrical response.

In cases of malignant hypertensive retinopathy a subnormal response can be recorded as a result of a greatly altered metabolic condition of the retina.

In the group with hypertensive sclerosis (Group 2) and that of diffuse atherosclerosis of the retina without hypertension (Group 3), showing the same minor retinal alterations and a similar distribution of cases over the various age groups, a definite difference in electrical response was met with when recordings were continued beyond the usual five-minute period of rest and dark adaptation. The incidence of subnormal responses is definitely lower in those cases showing an arterial hypertension (Group 2) than in those without hypertension (Group 3). Thus, it would appear that the hypertension is a useful mechanism by which the organism can compensate an otherwise insufficient nutrition of the retina.

In cases of diffuse atherosclerosis of the choroid the frequency of subnormal ERG's is highest. The discrepancy in these cases between the electroretinographic findings and the ophthalmoscopic picture suggests a more extended pathological process than can be revealed by the ophthalmoscope.

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ENZYMATIC CHARACTER OF RESPIRATION OF THE LENS

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THE PROBLEM of the respiration of the lens has been subjected to great study by Christiansen and Leinfelder. On the basis of several series of experiments, they have arrived at the conclusion that the respiration of the lens is a nonenzymatic process.

The maintenance of a normal oxygen consumption in spite of boiling the lens furnishes their principal argument. We decided it would be of interest to reexamine this important problem; therefore, we ask the following questions:

1. Does the boiled lens continue to consume oxygen?
2. Is this oxygen consumption of the same nature as that of the fresh lens?
3. What is the nature of oxygen consumption in the boiled lens?

To answer the first question, we homogenized 10 calf lenses in 10 cc. of water in a Waring Blendor. The mixture was poured into centrifuge tubes and heated in a salt-water bath while being shaken continuously. The heating was carried on for 40 minutes, and a temperature of 110 C. was reached.

Then the tubes were closed in a sterile manner and placed in an incubator at 37 C. for 24 hours to counter the objection that eventual differences of the Warburg manometer could be due to contraction of the coagulum.

The next day we centrifuged the tubes. The precipitate was suspended in 30 cc. of Krebs solution; 3 cc. of this was pipetted into Warburg flasks. Each flask thus contained the equivalent of one lens.

The fresh lenses which were used as controls were homogenized in 30 cc. of Krebs solution; 3 cc. of the homogenate was taken for each Warburg flask.

1. Proceeding thus, we found that during the initial seven minutes the oxygen consumption was the same in the fresh lens and in the boiled lens; sometimes it was a little less in the boiled lens. Subsequently, the amount of oxygen which disappeared in the flasks containing the controls was very much less than that which disappeared in the flasks containing the boiled preparations (Chart 1). By the method which we have followed (treatment at 110 C.) we obtained a deviation between the two curves which was much greater than that found by Christiansen and Leinfelder.

In this way it can be established that the boiled lens consumes oxygen, but that the rate of this consumption differs from that of the fresh lens. In the majority of

Translated from the French by Dr. J. S. Friedenwald, Baltimore.

cases there is a latent period during which the two curves are very close. But later the amount of oxygen consumed by the boiled lens is notably greated than that which is used by the fresh lens.

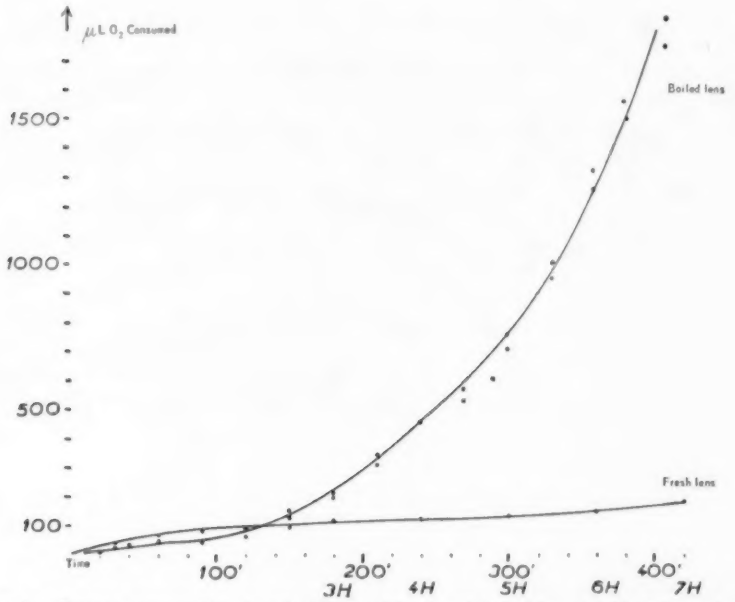

Chart 1.—Oxygen consumption, in microliters, of fresh and boiled lens (Table 1, Experiment 4).

TABLE 1.—*Oxygen Consumption of the Fresh and Boiled Lens During the First Hour* *

Exper. No.	Lenses	μM O_2 Consumption per Hour	μM Glucose Consumption per Hour	Lactic Acid Produced per Hour	μM O_2 / μM Glucose	μM O_2 / Lactic Acid
1	Fresh	2.9	4.5	...	0.65	....
	Boiled	11.2	2.0	...	5.6	....
2	Fresh	2.2	3.5	...	0.63	....
	Boiled	2.2	0.1	...	22.0	....
3	Fresh	2.2	3.9	...	0.57	....
	Boiled	9.8	2.0	...	4.9	....
4	Fresh	3.1	4.1	7.0	0.75	0.45
	Boiled	1.3	0.1	0.4	13.0	3.2

* The figures given per hour are the values for the first hour of manometric activity. The preparations studied anaerobically gave reasonably identical results.

2. We examined the consumption of glucose and the appearance of lactic acid in fresh and boiled lenses along parallel lines in an oxygen atmosphere and in a nitrogen atmosphere.

It is evident that both aerobically and anaerobically glucose disappeared much more rapidly in the fresh lens. In the boiled lens the consumption of glucose was sometimes negligible or nil. The amount of lactic acid appearing was insignificant in the boiled lens.

TABLE 2.—*Oxygen Consumption of the Fresh and Boiled Lens With and Without Addition of Lead Acetate*

Exper. No.	Lenses	Lead Acetate	μM O_2 Consumption per Hour	μM Glucose Consumption per Hour	Lactic Acid Produced per Hour	μM O_2 / μM Glucose	μM O_2 / μM Lactic Acid
1	Fresh	0	1.8	3.2	4.6	0.56	0.39
		+	1.1	0.0	2.8*	....	0.39
	Boiled	0	2.5	0.0	0.0	....	....
		+	1.1	0.0	0.0	....	....
2	Fresh	0	2.2	2.4	6.7	0.92	0.33
		+	1.8	0.0	1.9*	....	....
	Boiled	0	4.5	0.8	0.0	5.6	....
		+	1.3	0.0	0.0	....	....

* The lactic acid produced in the absence of glucose consumption undoubtedly originates in the intermediate components of glycolysis—hexosephosphate, triosephosphate, or pyruvic acid—normally present in the lens.

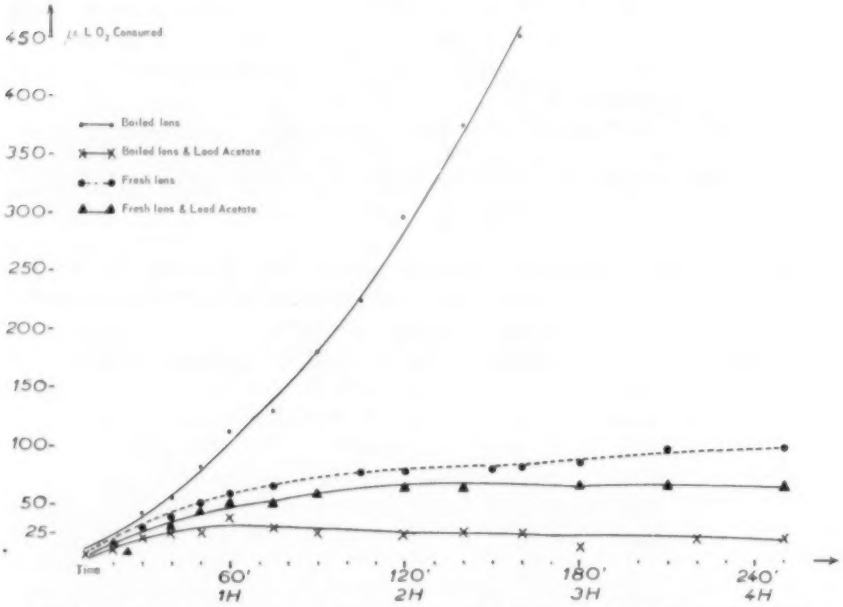

Chart 2.—Oxygen consumption, in microliters, of fresh and boiled lens with and without addition of lead acetate.

We can conclude from these observations that the consumption of oxygen occurs by different processes in the fresh and in the boiled lens. This holds true, moreover, for any tissue, for example, the liver; however, no one would dare to deny the enzymatic character of hepatic respiration.

3. We felt that the oxygen consumption of the boiled lens represents simply the phenomenon of auto-oxidation, not enzymatic oxidation. Suspecting in this auto-oxidation of the boiled lens the intervention of SH groups freed by the breakdown of protein molecules and the separation of the S–S bridges, we looked for an effect on the oxygen consumption of the boiled lens after the addition of lead acetate at a final concentration of M/20 to the flasks.

One can see, then, that the oxygen consumption of the boiled lens shows a considerable reduction. Its value clearly becomes less than that of the fresh lens and sometimes the same as that of the fresh lens with lead acetate added (Chart 2). There are probably SH groups present, appearing because of the denaturation of the protein molecules at the time of the boiling, which undoubtedly play a large part in the oxygen consumption. The more the denaturation is pushed, as in our case, the more the quantity of oxygen consumed is increased.

CONCLUSION

The consumption of oxygen by the boiled lens is of an auto-oxidative nature and depends on the denaturation of proteins. It cannot be compared with respiration in the fresh lens, which has characteristics distinguished by the consumption of glucose and the production of lactic acid.

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MITOTIC AND WOUND-HEALING ACTIVITIES OF THE CORNEAL EPITHELIUM

Effect of Sensory Denervation

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THE CLINICAL phenomenon of so-called neuroparalytic keratitis has commonly been assumed to be the expression of some trophic disturbance in the cornea consequent upon sensory denervation of this tissue. The fact that the catastrophic events of such keratitis can be avoided by blepharoplasty and the prevention of the cornea from drying does not disprove such a trophic influence. The purpose of the present study was to see whether neuroparalytic keratitis could be produced experimentally in animals and to find out whether after sensory denervation there was any change in the mitotic or wound-healing activities of the corneal epithelium.

Keratitis following injury to the trigeminal nerve has been reported by Zander and Weddell [1] in experiments on rabbits and monkeys and by Kotlyarevskaya [2] in cats. The latter author claims to have produced bilateral lesions following unilateral Gasserian ganglion injuries. In neither of these studies was the influence of sensory denervation on the mitotic or wound-healing activities of the tissues investigated. Previous studies in this laboratory [3] have shown that after excision of the superior cervical ganglion the rate of entrance into mitosis and the speed of the mitotic process were both slowed down. Since, however, there is no evidence of sympathetic innervation of the cornea, no conclusions could be reached as to whether this effect was a trophic one, or whether it was the indirect result of sympathetic denervation of the vascular tone, glandular secretion, etc., in the neighboring tissues.

Verhoeff [4] has suggested that diminution of lacrimal secretion after section of the trigeminal nerve may be the most important factor in eliciting the keratitis.

I. TECHNIQUE OF SENSORY DENERVATION

Our initial attempts at sensory denervation of the cornea consisted in the section of the ophthalmic branch of the trigeminal nerve by intracranial approach in rats. All the animals operated on died in 24 hours after intracranial hemorrhage. The results were the same whether the approach was intradural or extradural. The close proximity of the nerve to the great vessels at the base of the brain and the extreme friability of these vessels in the rat appear to preclude any reasonable percentage of operative successes by this method.

This study was supported by a grant from the American Cancer Society.

From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital.

In consequence of these failures we explored the possibility of damaging the nerve by diathermy cauterization. Anatomical investigations revealed that the nerve lay approximately 4 mm. above the roof of the mouth, that the base of the skull in this region could easily be punctured by a diathermy electrode, and that no vital tissues would be damaged in forcing the electrode through the tissues in the desired location. The roof of the rat's mouth possesses an easily identifiable landmark as a guide for the diathermy puncture. The anterior portions of the roof of the mouth are traversed by numerous transverse corrugations; the posterior portions are fairly smooth. The line of demarcation between the smooth and the corrugated portion is very sharp and quite regularly located. The optimal position for the puncture was found to be ⅛ to 3/16 in. (3.2 to 4.8 mm.) behind this demarcation line, and ⅛ in. lateral to the midline.

A diathermy electrode (Fig. 1) was made by grinding down the blade of a screw driver, yielding a sturdy instrument that could be firmly grasped by its wooden handle. The wooden handle itself provided adequate insulation for the operation. The penetrating pin of the electrode was 5 mm. long, tapering to 1 mm. in thickness near the tip and ending in a pyramidal and carefully sharpened point. The whole metal portion except the pyramidal tip was coated with Glyptal enamel (General Electric 1201).

Fig. 1.—Diathermy electrode photographed beside a centimeter scale.

Adult rats (150 to 200 gm.) were anesthetized with ether and tied, back down, to a small operating board. A rubber band passing just behind the upper incisor teeth served to hold the head firmly on the board. The lower jaw and tongue were retracted by another rubber band, attached to a movable stand, yielding good exposure of the roof of the mouth. Prior to placing the rat in this position, the fur on its back was moistened with soap solution, and the indifferent electrode of the diathermy apparatus was connected to a metal plate on the operating board, with which the moistened back of the animal was placed in contact.

In the initial experiments the electrode was forced into the desired position, and then the current turned on the coagulating level for one second. On withdrawal of the electrode under these circumstances, there was often profuse bleeding, chiefly from the nasal mucosa. Nevertheless, most of the animals survived this procedure. Later we found that if the current was applied during the whole period of insertion and removal of the electrode, the superficial hemorrhage was reduced to negligible amounts. The procedure requires a quick and firm movement, since application of the current causes a convulsive spasm. If the pressure on the electrode is not firm, the animal's head is likely to move slightly during the procedure and the target will be missed. The whole application can be accomplished in less than two seconds.

After the diathermy application, the animals were allowed to recover from the ether anesthesia and their blinking reflex was tested. The blinking reflex can easily be elicited on the normal side by touching the hair on the eyelids or by stroking the cornea with a wisp of cotton. The same test was repeated before any subsequent experimental manipulation. Any animals in which the blinking reflex was not repeatedly absent on the operation side were rejected as surgical failures.

At the termination of the experiment on each animal, the animal was decapitated and the head fixed in formalin. After fixation, the skull was opened and the brain removed. The position of the diathermy cauterization was usually easily seen (Figs. 2, 3, and 4). Its location could be confirmed by passing a small wire through the entrance hole in the roof of the mouth and noting its point of intracranial emergence. If the wire was not found to travel through the ophthalmic branch of the trigeminal nerve, the experiment was rejected. Photomicrographs of a section through an injured nerve are shown in Figures 5, 6, and 7.

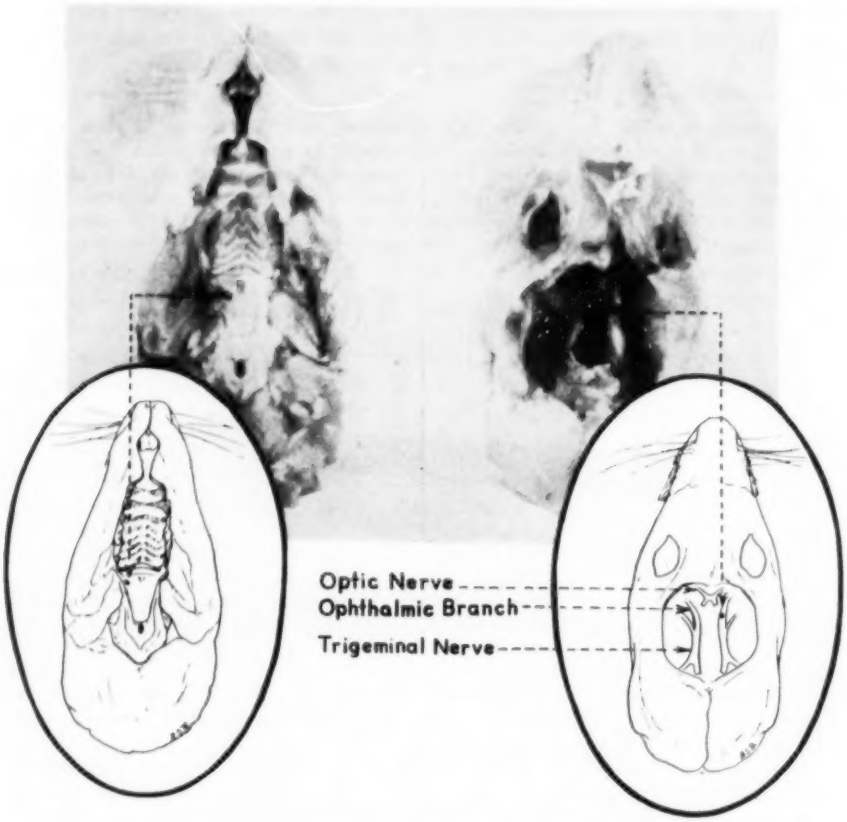

Fig. 2 (upper left).—Roof of rat's mouth showing entrance hole of diathermy cauterization.

Fig. 3 (upper right).—Base of rat's skull showing diathermy cauterization of ophthalmic branch of right trigeminal nerve.

Fig. 4 (lower left and right).—Schematic drawings of diathermy cauterization track.

After some practice an unexpectedly high percentage of successes was achieved. When one counts as failures all operative deaths, as well as all rejects because of failure to abolish the blinking reflex or failure to locate the puncture within the nerve, approximately 60% of the operations were successful. Routinely, the diathermy was made on the right side, the left side serving as a control.

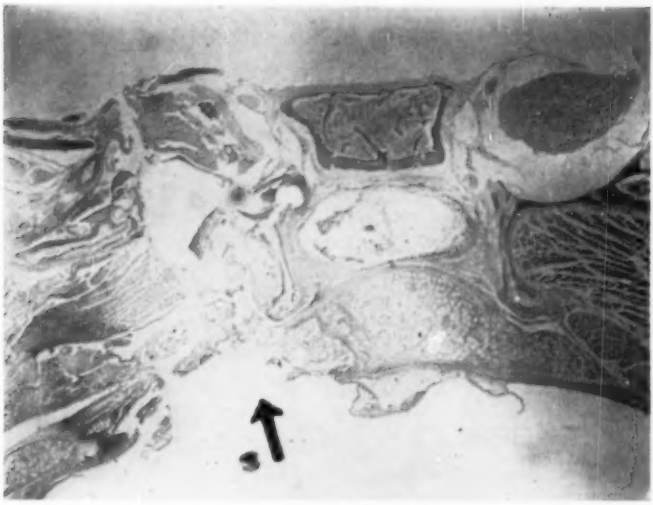

Fig. 5.—Photomicrograph of cauterization track through base of skull. The arrow shows direction of puncture.

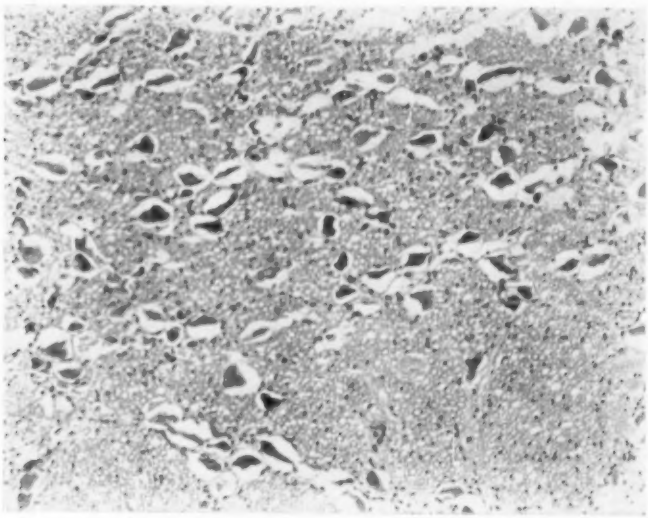

Fig. 6.—Photomicrograph of trigeminal nerve on left, uninjured side.

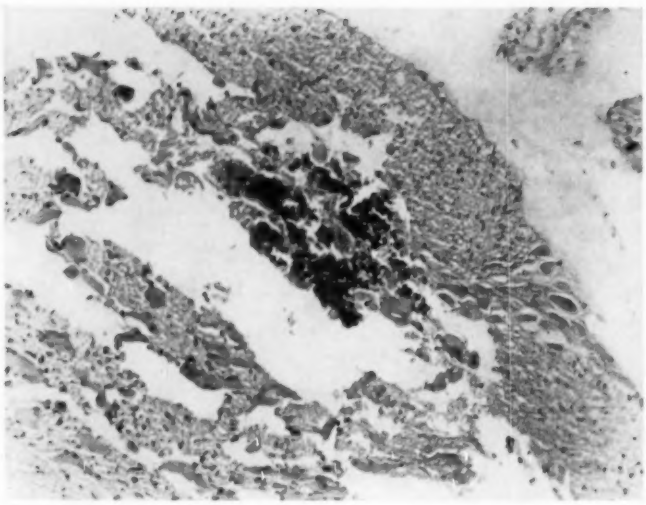

Fig. 7.—Photomicrograph of cauterized nerve three days after operation.

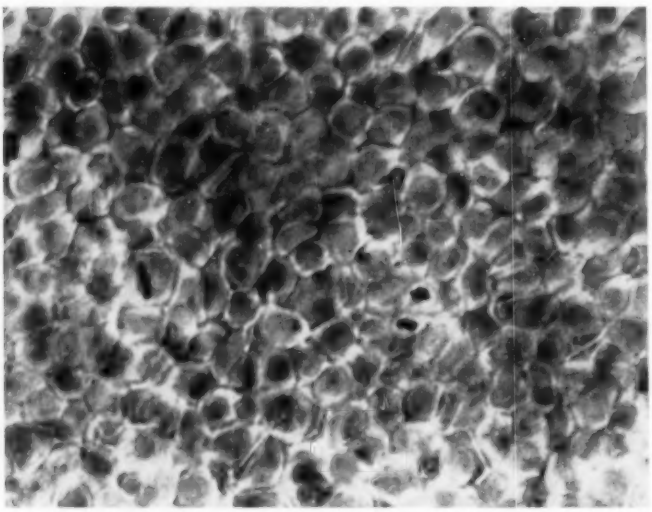

Fig. 8.—Flat preparation showing corneal epithelium on left, uninjured eye.

II. NEUROPARALYTIC KERATITIS

Postoperatively the animals were observed clinically, and their eyes were removed at varying postoperative intervals for microscopic study. Enucleations were performed under ether anesthesia, the eye on the intact side always serving as a control. Flat preparations were made by the technique previously described.[5]

Within three hours postoperative evidence of drying of the cornea in the interpalpebral fissure could be recognized histologically (Figs. 8 and 9). The epithelial cells in the exposed area appeared slightly shrunken, their nuclei being both shrunken and more deeply stained than in the control eyes or in the unexposed areas of the experimental eyes. Mitoses in the dried area were greatly reduced in number, and sometimes completely absent, but of apparently normal abundance in the unexposed areas.

These changes became more marked within the succeeding hours. Twenty-four hours after postoperation a diffuse purulent infiltrate was present in the corneal stroma (Fig. 10) in spite of the fact that no visible breaks or ulceration of the corneal epithelium was present at this time. By this time a slight clouding of the cornea could be recognized clinically on gross examination. The disease progressed rapidly from this point, with ulceration and perforation of the cornea in three to five days.

It is evident that the surgical procedure described above produces in rats an extremely severe and fulminating type of neuroparalytic keratitis.

III. MITOTIC ACTIVITY

The experiments reported in the previous section made it clear that drying of the cornea constitutes a major factor in the production of neuroparalytic keratitis in rats. If we are to seek any direct trophic influence of sensory denervation, this complicating feature of the experiment must be eliminated. In the following experiments, therefore, the animal's eyelids were sewed together on the denervated side immediately after the diathermy cauterization of the ophthalmic nerve and adequate testing to demonstrate the abolition of the blinking reflex. A single mattress suture in the center of the lids sufficed to secure closure. The control (left) eye in these animals was left open, since previous control experiments on normal rats had shown that sewing together of the lids of one eye was not followed by any difference in the mitotic activity in the corneal epithelium on the closed as compared with the open side.

Animals could be maintained for study as long as three to six days after the operation. With longer experiments, stitch abscesses developed about the lid-closing suture and the stitches often sloughed out. When this occurred, a fulminating keratitis developed, as in the animals without lid closures. It is to be regretted that longer-term experiments were not found feasible, but the duration of the study was surely sufficient to allow Wallerian degeneration of the peripheral portions of the nerve to have run its course. The distance from the point of diathermy cauterization to the nerve terminals in the cornea was not more than 10 to 12 mm.

At varying postoperative intervals both eyes of the animals were removed for microscopic study. Gross examination of the eyes after opening the lids revealed no difference between the denervated and the control eye. The specimens were prepared for mitosis counts according to a previously described technique.[5] In each animal

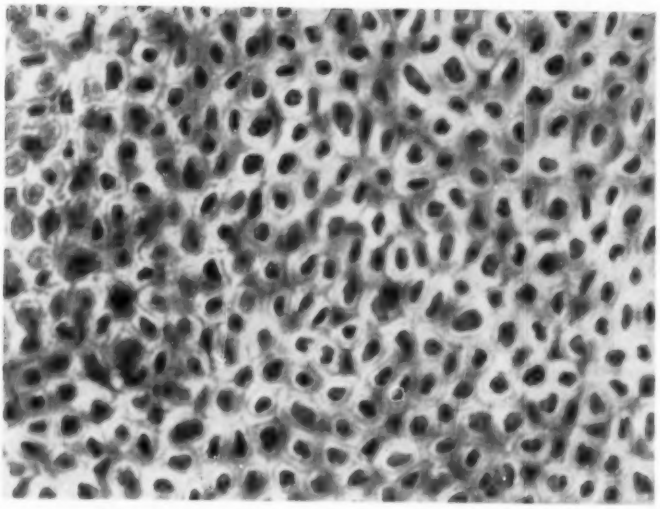

Fig. 9.—Drying of corneal epithelium four hours after sensory denervation.

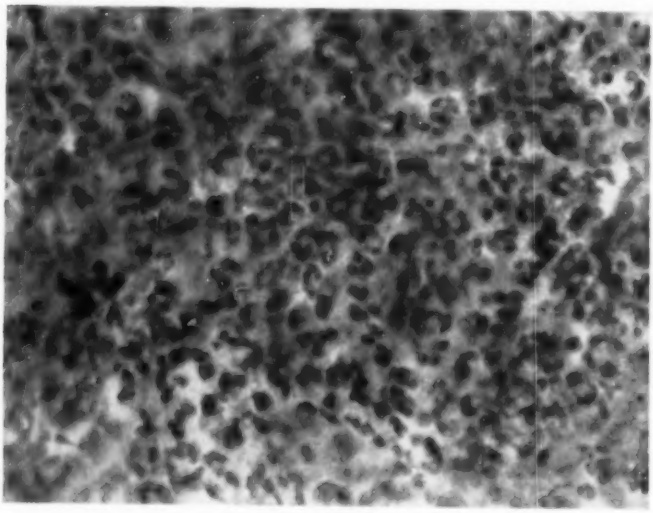

Fig. 10.—Purulent infiltrate in the corneal stroma one day after sensory denervation.

the left (undenervated) eye served as the control. The results, as will be seen in Table 1, show that, on the average, there are 12% fewer mitoses in the corneal epithelium of the right (operation side) than of the left eye. Previous studies [5] had shown that the standard deviation in mitosis count on the right versus the left cornea in rats is ±13%. Since the 12% difference noted in the data of Table 1 represents the mean of counts on 16 animals, this difference is statistically significant.

In previous reports from this laboratory on the mitotic activity of the rat's corneal epithelium, it has repeatedly been pointed out that the number of mitoses found in a standard area at a particular time furnished only a partial index of mitotic acitivity in the tissue. If the rate of entrance of cells into mitosis and the rate of their passage through the mitotic process are affected in the same proportion, the number of cells found in mitosis will still be normal. Entrance of cells into mitosis can be abruptly stopped by a variety of procedures that, under appropriate conditions, appear to have no effect on the rate of progress of cells through the mitotic cycle,

TABLE 1.—*Mitosis Counts* After Sensory Denervation of the Cornea: Right Eye Denervated; Left Eye Control*

Days After Operation							
One		Three		Four		Six	
R. E.	L. E.	R. E.	L. E.	R. E.	L. E.	R. E.	L. E.
98	86	58	82	120	102	129	131
83	85	52	60	158	80	118	130
117	119	142	155	89	126	...	...
104	86	169	250	167	156	...	...
26	110	97	133	...	...	...	...
144	124	183	244	...	...	...	...
130	115	123	171	...	...	...	...
35	91	215	184	...	...	...	...
737	816	1,037	1,279	534	524	247	261
Average 92	102	129	159	133	131	123	130

Average count of whole series: R. E., 116; L. E., 131

* The counts give the number of mitoses in a meridional strip 0.12 by 7.0 mm. in area across the cornea.

which in the rat's corneal epithelium has been shown to last approximately 70 minutes. Among the effective procedures for such experiments is the intramuscular injection of 0.15 cc. of a 1:1,000 epinephrine hydrochloride solution. With this procedure, the number of mitoses in the corneal epithelium of previously normal eyes declines steadily, reaching nearly zero at 70 minutes, at which time the few remaining mitotic figures are all in the late stages of the mitotic cycle. On the other hand, if in a given eye the rate of progress of the cells through the mitotic cycle is abnormally slow, then at 70 minutes after the arrest of cells from entrance into mitosis, there will still be found cells in mitosis in appreciable numbers, including some in prophase or metaphase.

The results of experiments of this type are shown in Table 2. These experiments showed a slight, but statistically significant, difference in the rate of passage of the cells through the mitotic cycle, the rate being approximately 10% slower on the denervated side. When these results are combined with those shown in Table 1, we conclude that the rate of entrance into mitosis is about 20% slower on the denervated than on the normal side.

In a previous study,[7] we have shown that the mitotic mechanism in the rat's corneal epithelium is extremely sensitive to x-radiation. It seemed possible that some subtle effect of the denervation might be revealed in the reaction of the cells on the denervated side to x-radiation. A dose of radiation (32 r, 5 ma., 85 kv., 3 mm. Al filter) was chosen which in normal animals had produced only a partial

TABLE 2.—*Mitosis Counts Three Days After Denervation (Right Side) and Seventy Minutes After Intramuscular Injection of 0.15 Cc. of Epinephrine Hydrochloride (1: 1,000)*

R. E.	L. E.
12	6
8	4
8	2
23	9
24	8
25	13
26	2
28	28
14	8
18	21
36	14
23	22
245	130
Average 20.4	11.0

TABLE 3.—*Mitosis Counts After Exposure to X-Rays and Denervation (Right Side) Twenty-Four Hours Before X-Irradiation*

Hours After Exposure			
Two		Four	
R. E.	L. E.	R. E.	L. E.
11	22	52	66
85	102	74	36
77	29	152	163
24	56	166	203
39	81	159	153
48	26	187	193
44	51	175	157
123	111	165	188
155	121	..	..
150	116	..	..
82	50	..	..
60	59	..	..
898	884	1,130	1,150
Average 74	73	141	143

inhibition of mitosis, yielding mitosis counts that at first declined somewhat below the normal and then recovered, temporarily overshooting the normal. The trough of decline and the peak of overshooting in the normal animals with this dose of radiation were at two and four hours after exposure, respectively. Exposure to radiation was made without anesthesia, using the rat holder devised for this purpose and previously described.[7]

Table 3 shows that the degree of inhibition of mitosis two hours after x-irradiation was the same in the denervated as in the control corneas. Recovery from the radiation inhibition was also equal in the two eyes four hours after exposure.

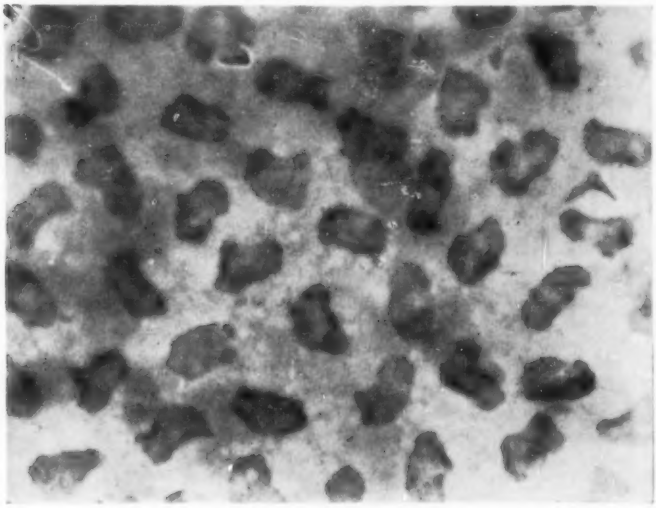

Fig. 11.—Corneal endothelium of left, uninjured eye.

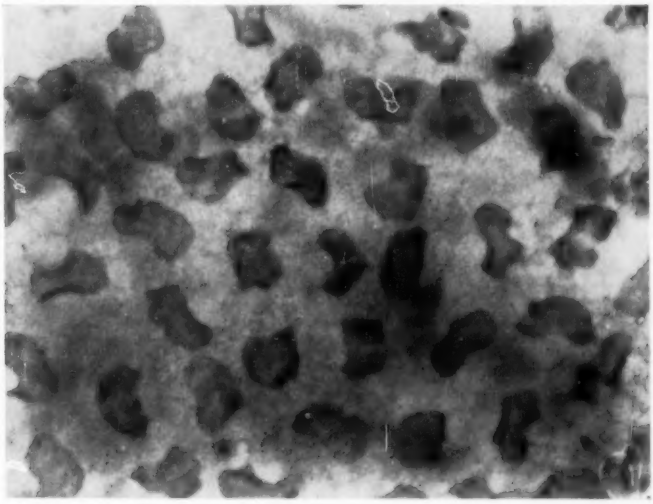

Fig. 12.—Corneal endothelium of right eye 24 hours after denervation. The lids had been sewn together immediately after denervation.

In all these experiments the microscopic appearance of the corneal stroma cells was also studied, and no difference was noted between the denervated and the control corneas. No abnormalities in structure or number of cells of the corneal endothelium were noted (Figs. 11 and 12).

IV. WOUND HEALING

In previous reports[6] from this laboratory, a method of producing pinprick wounds in the rat's corneal epithelium has been described, and observations on the healing of these lesions in normal and in various abnormal conditions have been reported. We have applied these methods in the present study. Diathermy cauterization of the right ophthalmic nerve and closure of the lids on the denervated side were performed as described above. At varying times postoperatively the lid suture was removed and the animal tested for blinking reflex. If the results of this test

TABLE 4.—*Healing* of Pinprick Wounds in Corneal Epithelium One Day After Sensory Denervation on Right Side*

	3+	3−	2+	2−
Three-hour experiment				
R	10	5	..	..
L	10	3	..	1
R	12	..	..	..
L	5	3	3	5
R	8	3	..	..
L	8	6	1	..
R	11	6	2	..
L	17	1	1	..
R	12	5	..	..
L	10	3	4	..
Two-hour experiment				
R	..	..	10	5
L	..	..	4	21
R	6	1	6	..
L	5	8	13	..
R	2	..	11	1
L	1	3	10	3
R	1	2	10	..
L	1	5	4	7

* In evaluating the rate of healing of the wounds, the following standard was followed: 3+, floor of wound completely healed and no tangential cells present in top layer; 3−, floor of wound completely healed but tangential cells still present in top layer; 2+, floor of wound not completely closed but all basal cells at wound margin arranged radially; 2−, tangential cells still present in floor of wound. After three hours the normal eye contains a majority of wounds in the 3+ stage. After two hours the majority of the wounds in a normal eye are in the 2+ stage or better.

showed anesthesia on the denervated side, the animal was anesthetized with ether, and both corneas were stippled with 30 or more pinpricks. The lids on both sides were then closed with mattress sutures. Two and three hours after the pinpricking, the animals were killed and both eyes removed for microscopic study. Previous studies on normal animals had shown that at two hours after pinpricking, almost all the pinprick had begun to heal, whereas at three hours after the injury, healing was complete in almost all the lesions. The results of these experiments are shown in Table 4. No significant difference was found between the healing of the epithelial wounds in the denervated and in the control corneas. Moreover, there was no sig-

nificant difference in the rate of healing of these wounds under closed lids, as compared with our previously reported experiments on normal animals, in which the eyes were allowed to remain open after the pinpricking.

SUMMARY AND CONCLUSIONS

A diathermy coagulation procedure is described by which the ophthalmic branch of the trigeminal nerve in rats can be severely damaged.

After successful operations there is complete loss of the blinking reflex on the operation side.

A fulminating and severe form of neuroparalytic keratitis results. Some of the characteristics of this lesion are described.

The keratitis can be prevented by closure of the eyelids. It is, therefore, a form of exposure keratitis. Whether the exposure keratitis is determined solely by absence of blinking or is aggravated by diminished lacrimal secretion was not determined.

In the denervated cornea protected from exposure by lid closure, the mitotic rate was diminished approximately 20% and the wound-healing activities of the corneal epithelium were normal. Sensitivity to mitotic inhibition by ionizing radiation was not altered. No histologic abnormalities were noted in the corneal stroma, endothelium, or epithelium.

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FIVE-YEAR SURVEY ON USE OF A MAGNETIC IMPLANT FOR IMPROVING COSMETIC RESULT OF ENUCLEATION

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FOR THE past five years, since April, 1948, I have advocated and employed a magnetic implant for improving the cosmetic appearance of enucleation patients. Preliminary reports have been given before the Section of Ophthalmology of the New York Academy of Medicine,[1] and the XVI. International Congress of Ophthalmology.[2] A statistical survey covering the use of 1,509 implants of this and other types has been presented before the American Academy of Ophthalmology and Otolaryngology.[3] I feel that after five years it is time for a definitive report on the use of the magnetic implant.

This implant was devised to combine the advantages of the completely covered spherical implant and the advantages of the uncovered motility implants while eliminating, at least to some extent, the disadvantages of both the other types in use. The spherical implant, as we all know, is highly satisfactory surgically; however, postoperatively, except for the minimum discharge, it leaves much to be desired cosmetically. It is still, however, the choice of the majority of ophthalmologists in this country and in Europe. The semiburied motility implant is well known to all of us. Its excellent cosmetic result has been a prime stimulus to development of new operative techniques for enucleation. A number of implants of this type have been proposed.[4] The disadvantages of this type of implant are (1) severe postoperative discharge, (2) tendency toward frequent infection of the socket, (3) delayed extrusion or displacement of the implants, necessitating removal (occurring in 28% of my reported cases and in as high as 50% in some series reported to me), and (4) rotation of the implant to such a position that the effectiveness of the pin integration is lost and the immediate good result nullified.

It is well recognized that, despite partial success in solving these problems, the weight of opinion is still that the covered type of implant gives less patient difficulty and less need for prolonged postoperative care by the ophthalmologist.

The magnetic implant is completely buried and employs several forces to produce motility. First, and the reason for its development, is the use of magnetic attraction between the implant and the prosthesis, eliminating the necessity for exposure through contact with a peg. This allows the use of a modified "motility" type of prosthesis and prevents excessive pressure in the cul-de-sac, and thus on the muscle attachments, in extreme rotations of the eye. Second, the flat anterior surface, when apposed to the flat posterior surface of the prosthesis, acts as a fulcrum, forcing the eye in the direction of rotation of the implant while the cul-de-sac is being retracted

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before it. Third, the implant is attached directly to the four rectus muscles, so that it will remain in essentially the same position throughout the life of the patient. The problem of migration, such as occurs with spherical implants, is thus solved, and the configuration of the socket, and thus the motion, remains more constant. Several other implants, notably the Allen type, employ two of the three principles mentioned, with excellent results.

The cases to be reviewed are those of unselected enucleation patients from the New York Hospital-Cornell Medical Center and the Manhattan Eye, Ear and Throat Hospital operated on over the past five years by my associates and myself.

Of a total of 102 implants, 98 were primary and 4 secondary. The percentage of the total number of implants placed during each year of the survey was estimated. A follow-up of one year or longer was obtained on 68% of patients, 27% being followed three years or longer. A mortality rate of 10% of all patients was discovered on examination of hospital records.

Motility requires definition before the figures may be accurately analyzed. I consider a patient to have 60–80% "motility" if his horizontal motility is 20 degrees to either side of the primary position and his vertical motility is 15 degrees to either side of the primary position. Other considerations are good cosmetic appearance, "quick motion" of the eyes in the primary position, and absence of lid sulcus, ptosis, or stare. The largest percentage of patients falls in this group according to my observation. The figure of 63% differs significantly from that which I reported in 1951 for this category, being then 30%. The 80–100% group was reported at that time as 35%, as opposed to 26% in this series. In the present series, which was more closely controlled, we had the advantage of repeated examination of many patients and close cooperation of the eye maker in the fitting of the prosthesis, factors which added measurably to the results. We found that many patients did not have an immediate good result. However, if they were refitted in from three to six months, and in several cases one year, after surgery, considerable improvement could be obtained. This was attributed to the enlargement of the socket, making it possible to fit a larger eye, with incorporation of a magnet, where before only a shell eye could be fitted. The question arises as to whether the magnet makes any significant difference in the motion. Observation indicates that it does add to the cosmetic result. About 30% of patients still do not have magnets incorporated in their prostheses. These fall mainly in the lower categories. The careful fitting of a good artificial eye with a flat posterior surface in apposition to the implant gives good motility without a magnet, though rarely does it enter the 80–100% group. Addition of a magnet allows the eye to be slightly smaller, and thus gives it a greater range in the cul-de-sac, which is relieved in part of the necessity of providing support. The need for continuing care by the eye maker should be stressed to the patient, who has usually been led to believe that he or she has a "permanent eye." Minor adjustments from time to time may make a great difference in appearance. It should also be stressed to the patient, before operation if possible, that even at best the eye is an artificial one and that the most perfect result may leave something to be desired. I do not feel that a full range of motion is essential for good cosmetic appearance and function. The one-eyed person usually makes little use of his temporal range of motion because on rotating his normal eye nasally he cuts his visual field and begins to turn his head. The patient soon learns to

correct for any loss of motion in other directions by turning the head instead of the eye. If he fails to do this, he can be instructed by the ophthalmologist or the eye maker. The important considerations are good "quick motion" in conversation, a normal lid contour, and well-matching prosthesis.

Figure 1 shows a patient who represents several types of motility. On looking down the motion is excellent; the lid, however, is slightly distorted. On looking up, the motility is minimal, with good lid contour (Fig. 2). In eyes left (Fig. 3), moderate (40%) motility is exhibited, with good lid contour. With eyes right

Figure 1

Figure 2

Figure 3

Figure 4

(Fig. 4) there is 100% motility and good lid contour. This patient would be classified in the lower 60–80% group, as he has good cosmetic appearance and good "quick motion." The second patient (Fig. 5) shows a similar nasal motility, excellent temporal motility (Fig. 6), and excellent cosmetic appearance (Fig. 7). He, too, would be classified in the lower 60–80% group. The socket of the second patient is representative of those being obtained (Fig. 8). This patient had only minimal discharge.

The occurrence of ptosis and deep sulcus, I feel, is related to defective surgical technique. Their incidence is minimal in the series. A deep sulcus is seen to some degree in almost every enucleation patient; however, I include only those which are cosmetically disfiguring to the patient. To prevent such a condition, I carry out a thorough dissection of the superior rectus from the levator palpebrae

superioris. This prevents the mechanical retraction of the lid, producing a deep sulcus, and prevents the mechanical fixing of the levator to the superior rectus tendon, producing stare or pseudoptosis.

The percentages of extrusions and removals in the series are markedly higher in the first year. During the past three years the average has been only 4%, which is the same as that reported in the Academy survey for spherical implants. Between 1949 and 1952, at Manhattan Eye, Ear and Throat Hospital, 243 spherical implantations were performed. On reviewing these cases, it was found that 8, or

Figure 5

Figure 6

Figure 7

Figure 8

3%, of the implants had been extruded. No figure on displacement of the sphere within the orbit was obtained. This has not occurred, however, with the magnet implants.

The incidence of uncovering of the implant was higher in the first two years of the survey and has been almost nonexistent in the last three years. I should like to stress the importance of immediate closure of exposed implants of any type. This is an operating-room procedure, and a careful dissection and layered closure are essential. Delayed closure may be impossible or result in shrinkage of the cul-de-sac.

Discharge, again, requires definition of terms. Minimal discharge indicates that the patient is comfortable at all times and cleans his socket for hygienic reasons only. Moderate discharge is somewhat annoying to the patient and requires wiping the eye several times daily, usually not in excess of five, with frequent hygienic

cleansing of the socket, up to three times a day. By severe discharge is meant the constant mucopurulent discharge, which is a continuous source of annoyance to the patient and requires antibiotic therapy for control. These Figures represent a major statistical difference from the Academy report of the exposed implants, 15% of which showed severe discharge and 21% moderate discharge.

Allergic reactions were uncommon. In the one case reported the response to cortisone and control of a neglected (by the patient) secondary infection has been good.

Granulation tissue occurred minimally in four sockets. It was treated by cauterization and did not recur.

SUMMARY

A magnetic implant for use after enucleation is presented. This implant employs some of the principles of the pin-integrated implants, the most important of which we believe is the positive fixation of the implant to the extraocular muscles. We have retained the surgically sound principle of completely burying the implant, relying on the shape and the magnetic principle to furnish integration. We have attained motion, which, though not as great as that obtained as an immediate result in integrated implants, is nevertheless reproducible in a large series of cases, with far fewer complications over a prolonged follow-up. The surgical technique employed is a part of the Scientific Exhibit and will be presented for publication. I believe this implant or similar implants which are positively fixed to the extraocular muscles and completely buried should be used in all cases in which a maximum cosmetic result with a minimum of postoperative difficulty is desired.

430 E 63d St.

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ADULT OCULAR TOXOPLASMOSIS

Report of a Parasitologically Proved Case

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WITHIN recent years the question of the toxoplasmic etiology of uveitis has been the subject of various surveys and investigations. Frenkel [6] (1951) found a correlation between skin test reactions and uveitis in a small group of hospital patients in California. Frenkel and Friedlander [7] (1952) presented the results of the dye test of Sabin and Feldman [13] on the same patients; they found most of the antibody titers to be low and postulated that the parasites could reside in the eye over long periods without stimulating antibody production. Hogan [8] (1951), because of lack of correlation between serological findings and adult uveitis, considered it unlikely that many cases of adult uveitis are due to toxoplasmosis. Hogan, Thygeson, and Kimura [9] (1952) later found the incidence of positive dye test reactions higher in patients of all age groups with chorioretinitis than in other groups, but in most cases the titers were low; Hogan, in attempting to explain this, suggested that possibly Toxoplasma strains of low virulence exist which are capable of producing a severe uveitis without stimulation of antibody production. Franceschetti and Bamatter [4] (1953) have reviewed most of the literature on this point and have discussed the uncertainties regarding the importance of acquired toxoplasmosis in the etiology of uveitis.

Feldman * (1952) emphasized these doubts in discussing the paper of Hogan and associates,[9] and also in a separate report [3] (1953). He found no correlation between chorioretinitis and the presence of anti-Toxoplasma antibodies. Sabin [14] (1953), in commenting on the question, maintained that such serological evidence as was available indicated that most cases of uveitis in adults were not of toxoplasmic etiology.

Woods, Jacobs, Wood, and Cook [18] (1954) presented a study of a large series of cases in which it was found that there was a strikingly higher incidence of positive

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* Feldman, H. A., in discussion on Hogan, Thygeson, and Kimura.[9]

dye test reactions among patients with granulomatous uveitis unassociated with any evidence of other etiology than in control groups. Here again, however, the dye test titers were generally low. Despite the low titers, these authors concluded that toxoplasmosis could account for about 25% of cases of granulomatous uveitis. Fair [2] (1954), in a general discussion of uveitis, presented serological data on cases of possible adult ocular toxoplasmosis and expressed the belief that some of the cases, at least, had to be considered as of toxoplasmic etiology.

The most definite evidence has been Wilder's report [17] (1952) of the presence of protozoa in chorioretinal lesions of eyes enucleated because of pain and blindness due to a granulomatous uveitis originally considered "probable tuberculosis" on a pathologic basis. The resemblance of these parasites to Toxoplasma was beyond question. However, the total number of cases from among which these 53 cases were culled was not reported. Moreover, since other parasites of similar appearance exist, the identification of Toxoplasma must be made on the basis of biologic and immunologic, as well as morphologic, criteria. Jacobs, Cook, and Wilder [12] (1954) traced 21 patients in whose eye lesions these parasites had been discovered by Wilder and found positive dye test reactions in all. They concluded that this serological evidence favored the identification of the organisms as Toxoplasma, even though practically all the patients showed only low dye test titers. They explained the low antibody levels on the postulate of Frenkel and Friedlander that the localization of the parasite in the eye after its disappearance from other parts of the body could result in little antigenic stimulation. As corollary evidence in support of this postulate, they cited the demonstration, in survey work, of Toxoplasma in the tissues of wild rats (Eyles,[1] 1952) and wild pigeons (Jacobs, Melton, and Jones,[10] 1952) which were negative serologically, and the same finding in experimentally infected pigeons kept for several years after inoculation (Jacobs, Melton, and Cook,[11] 1953). They recognized, however, that the ultimate demonstration of the toxoplasmic etiology of uveitis in adults would have to come from the isolation and identification of live parasites from typical cases.

It is the purpose of this report to present such direct evidence.

REPORT OF CASES

A. J. H., a 30-year-old white male Army sergeant, was first seen in the Eye Clinic, Walter Reed Army Hospital, on Dec. 11, 1953. He had been hospitalized elsewhere for three months because of chronic uveitis and secondary glaucoma. There had been no trouble with either eye until eight and a half years before, when, while he was on active military duty in Australia, there first appeared haziness of vision in the left eye. A diagnosis of chorioretinitis was made, and vision slowly improved until a few months later, when the inflammation recurred and central vision in the left eye was lost. Typhoid vaccine was used intravenously, and finally the patient was evacuated to the United States, where he was discharged from the Army because of his disability.

Three years later, the patient developed malaria and hepatitis in Guatemala. He returned to the United States and was hospitalized for several months. During his hospital stay, the inflammation in the left eye recurred and then slowly subsided. In September, 1953, while he again was on active duty in the Army, he had severe pain in the left eye and was again hospitalized. At this time, there were described injection of the conjunctival vessels of the left eye, deposits on the posterior surface of the cornea, heavy flare and many cells in the aqueous, posterior capsular and subcapsular cataracts, and large floating vitreous opacities. The fundus could be made out in only a hazy fashion, but it was thought that two areas of chorioretinitis were seen, one in the region of the macula and another nasal to the disc. The vision in the left eye was reduced to 5/400. The right eye was normal aside from a small astigmatic error.

During this hospitalization, streptomycin, 1 gm., and paraaminosalicylic acid, 4 gm., were given daily for 34 days. The intraocular tension rose and fell, and the signs of active inflammation continued. A posterior synechia formed, secluding the pupil, and retinal detachment followed.

Finally removal of the eye was advised, and the patient was transferred to Walter Reed Army Hospital. General physical examination was normal, as were the routine laboratory and x-ray studies. The right eye was normal. In the left eye vision amounted to faint light perception. Mutton-fat precipitates dotted the lower half of the cornea. There was a heavy aqueous flare, but no floating particles. The pupil was secluded. Clumps of pigment had proliferated on the anterior lens capsule. There was a dense posterior subcapsular cataract, which prevented a view of the fundus. A second search for foci of infection revealed only poor oral hygiene and a 3+ skin test, using second-strength tuberculin U.S.P.; skull x-rays showed no intracerebral calcification. The Sabin-Feldman dye test for toxoplasmosis on serum taken on Dec. 14, 1953, was reported as positive in a dilution of 1:64. The skin test for toxoplasmosis, done on the same day, was strongly positive (2 cm. of induration, surrounded by another 2 cm. of erythema). Dye test titers two and seven days following the skin test remained unchanged at a dilution of 1:64.

The past history included the usual childhood diseases and weakness of the legs at the age of 11, for which no cause was determined. There was, in addition, a history of malaria and dysentery in the South Pacific in 1944-1945 and of hepatitis and malaria in 1948. The patient's father died at age of 57 of Hodgkin's disease. His mother has diabetes but is otherwise well. One brother and two sisters are living and well.

On Jan. 12, 1954, the affected eye was enucleated. At the time of operation the globe was sectioned and its interior inspected. The vitreous was fluid and the retina completely detached except at the ora serrata and the posterior pole. Folding of the retina and the fresh state of the eye prevented a thorough examination, but there could be made out a smooth, gray disciform opacity lying in the retina posteriorly and attached to the underlying choroid. An attempt at division of this lesion was decided against, and the half of the globe in which it was found was used in the isolation studies described below. The remaining half of the eye was fixed immediately in 10% formalin solution for pathological examination.

ISOLATION OF THE PARASITE

Immediately after the division of the globe, the half of the eye to be used in the isolation studies was taken from the operating room and handled precisely as follows: The inner layers were separated from the sclera and, together with the liquefied vitreous, were macerated in a sterile mortar with the addition of a small amount of isotonic saline. Four mice were then inoculated intracerebrally with 0.02 ml. of the resulting suspension with the use of a short 27-gauge needle. In the second step, with the use of a sterile Pasteur pipette, two or three drops of the suspension were added to each of four roller tube tissue cultures of chick embryo heart muscle and to each of four roller tube cultures of minced mouse embryo tissue. The syringe used for the intracerebral inoculations of the mice was then fitted with a sterile long 24-gauge needle, which was used to inoculate the yolk sacs of two chick embryos. One of these embryos received 0.25 ml. and the other 0.5 ml. of the inoculum. The same needle was then used to give intraperitoneal inoculations of 1.0 ml. of the suspension to the mice previously inoculated intracerebrally and to two additional mice. Thus, by these careful procedures, avoidance was assured of even the remote possibility that contamination of the inoculating instruments in one spontaneously infected animal might result in the appearance of Toxoplasma in the other media subsequently injected.

Two days after these inoculations, it was necessary to renew the nutrient fluid in the roller tube tissue cultures. The old fluid was removed, pooled, centrifuged at low speed, and resuspended in a small volume of the supernatant, and the six mice described above were inoculated in 0.25 to 1.0 ml. amounts. Five days after inoculation, the chick embryo which received 0.25 ml. of the suspension of ocular tissues was found dead; a microscopic examination of its membranes and brain failed to reveal toxoplasmas; nevertheless, 1.0 ml. of the suspension was injected intraperitoneally into each of two fresh mice. Seven days after inoculation, it was again necessary to renew the nutrient fluid in the tissue cultures; the old fluid from the four tubes in each series was pooled, centrifuged at low speed, resuspended in part of the supernatant, and injected intracerebrally (0.02 ml.) and intraperitoneally (1.0 ml.) into each of two fresh mice.

The results of these procedures were practically universally successful. All six of the originally inoculated mice died on the seventh day following inoculation. All were found to have toxoplasmas in the peritoneal exudate, which was plentiful in all the mice. The chick embryo which received 0.5 ml. of the uveal tract suspension was alive on the eighth day after inoculation. It was opened at that time, and toxoplasmas were easily demonstrated microscopically in a fresh preparation of a suspension of its membranes. The eye of the embryo presented whitish lesions, which are shown in Figure 1; scrapings from these lesions also contained the parasites. The mice inoculated with material from the chick embryo that died on Day 5 died of toxoplasmosis in 12 to 15 days. The tissue cultures, both of mouse and of chick embryo origin, were also found positive for Toxoplasma; the first positive culture was found on the eighth day, and all were shown to be positive on the ninth day by microscopic examination of the nutrient fluid. In addition, the mice inoculated with the nutrient fluids of these cultures also died of toxoplasmosis in 11 or 12 days.

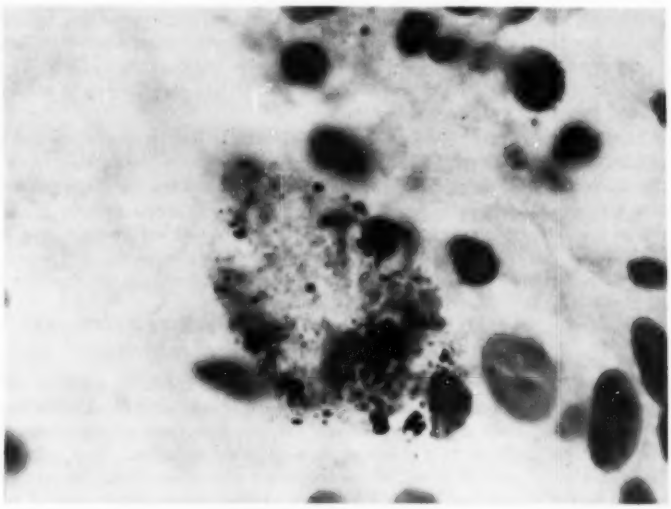

Fig. 1.—Chick embryo removed from shell eight days after yolk sac inoculation with 0.5 ml. of human ocular tissues from Patient A. J. H. The whitish spots above the eye were found to contain toxoplasmas.

The newly isolated strain of the parasite has been designated as the AJH strain. It is being maintained in mice, chick embryos, and tissue cultures.

IDENTIFICATION OF THE PARASITE

The morphology and behavior of the parasite thus isolated were sufficiently characteristic of Toxoplasma gondii to make us practically certain of its identity. Nevertheless, in order to establish this point beyond any question, a number of procedures were carried out.

Two rabbits were inoculated with 5,000 parasites each from the peritoneal exudate of one of the original mice. The inoculations were made intradermally in five spots, each receiving 0.1 ml. containing 1,000 organisms. One of these animals, Rabbit 395, had survived a previous inoculation two months earlier of 2,000 toxoplasmas of an avirulent strain; the other, Rabbit 411, was a fresh animal. Rabbit 411 died of toxoplasmosis on the 10th day after this inoculation; Rabbit 395 is still alive. The lesions which were produced on the backs of these animals by intradermal inoculation are shown in Figure 2; the photographs were taken on Day 10,

the day of death of Rabbit 411. It can readily be seen that the lesions on Rabbit 395 were minimal as compared with the large areas of induration, with ischemia and beginning central necrosis, seen on Rabbit 411.

Similarly, cross immunity was tested in guinea pigs. Three fresh and three immune guinea pigs were inoculated intraperitoneally with 10,000 toxoplasmas of Strain AJH. The immune

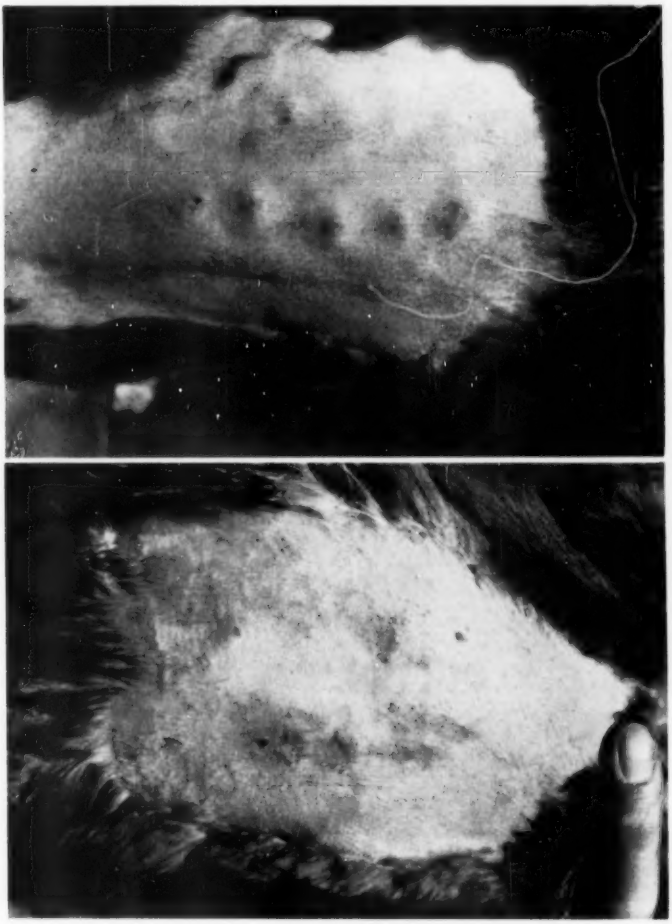

Fig. 2.—Results of intradermal inoculation of parasites of Strain AJH of T. gondii in (*a*) fresh rabbit 411 and (*b*) immune rabbit 395.

guinea pigs had survived a previous infection four months earlier with a relatively avirulent strain of Toxoplasma. The fresh guinea pigs succumbed to the AJH infection in 7 to 10 days. Of the three immune animals, one died on the 19th day after inoculation with the AJH strain, and the others manifested no symptoms and were still alive two months later.

Strain AJH also reacted in a manner practically identical to the RH strain of Toxoplasma in parallel runs of the in vitro dye test with the same positive sera, including serum of the patient from whom the strain was isolated. The details of this test are presented in Table 1.

The sera tested showed approximately the same titers with either strain of parasites, the differences being no greater than might occur in two different tests of a serum with the same strain of Toxoplasma.

SEROLOGICAL HISTORY OF THE PATIENT

It has already been stated that approximately one month prior to enucleation the dye test titer obtained on the serum of this paient was 1:64, and the toxoplasmin skin test was strongly positive. One week following enucleation, another specimen of serum was obtained and was found to have a surprisingly high dye test titer, 1:4,096. Thereafter, specimens were obtained at weekly intervals and tested in parallel runs with those obtained earlier. The results are summarized in Table 2.

TABLE 1.—*Comparison of Dye Test Findings in Parallel Runs with the RH and AJH Strains as Sources of Parasites*

	RH Parasites						AJH Parasites					
	Source of Serum						Source of Serum					
Dilution of Serum*	LJ		AJH		Rabbit 5		LJ		AJH		Rabbit 5	
	S†	U†	S	U	S	U	S	U	S	U	S	U
0	..	..	<5‡	>95‡	..	..	..	..	<5	>95	..	..
16	<5	>95	<5	>95	..	..	10	90	12	88	..	..
64	<5	>95	30	70	<5	>95	12	88	17	83	5	95
256	43	57	>95	<5	<5	>95	38	62	87	13	5	95
1,024	>95	<5	..	..	<5	>95	87	13	..	..	5	95
4,096	..	..	..	..	61	39	..	..	..	..	49	51
16,384	..	..	..	..	>95	<5	..	..	..	..	89	11

* The dilution of serum given is the original dilution before its being mixed with the other ingredients of the dye test reaction mixture.

The reaction mixture was as follows: 0.1 ml. of the dilution of serum and 0.1 ml. of a 1:5 dilution in normal human serum of the peritoneal exudate of Toxoplasma-infected mice, incubated for one hour in a water bath at 37 C. On removal from the water bath, 0.1 ml. of alkaline methylene blue solution was added to each tube. The methylene blue solution was prepared by adding 0.3 ml. of saturated alcoholic methylene blue to 1.5 ml. of soda-sodium borate (borax) buffer, pH 10.8 (prepared from Coleman buffer tablets). Drops from each tube were then examined microscopically.

† S and U refer, respectively, to the percentages of stained and unstained parasites seen in the reaction mixtures with the designated serum dilutions.

‡ The figures <5 and >95 indicate that the preparations showed such a predominance of either stained or unstained parasites that there was no need to make a count, and such preparations were judged by inspection.

TABLE 2.—*Dye Test Titers Obtained on Serum of A.J.H. Prior to and After Enucleation of His Left Eye on Jan. 12, 1954, Because of Toxoplasmic Chorioretinitis*

	1953			1954					
Date	12/14	12/16	12/21	1/19	1/26	2/2	2/9	2/16	2/23
Titer	1:64	1:64	1:64	1:4,096	1:128	1:1,024	1:256	1:256	1:256

The complement fixation test, done by the Immunology Section, Laboratory of Tropical Diseases, National Microbiological Institute, was performed on all specimens up to and including that obtained on Feb. 23, 1954. The test was consistently negative.

A specimen of serum was also obtained from the mother of A.J.H. on Feb. 9. It reacted positively at a titer of 1:8 in the dye test and negatively in the complement fixation test.

PATHOLOGICAL FINDINGS

The following gross findings were recorded on examination of the enucleated eye. The eye was of normal size and shape. No evidence of inflammatory invasion of the episclera or sclera was noted. The first calotte was taken in the horizontal plane on the nasal side. The retina and vitreous were detached, and the vitreous was cloudy. Two lesions were noted on the lateral side of the eye. The larger lesion was near the macula, while the second lesion was near the ora serrata. The eye was bisected, and the lateral half, including the cataractous

lens, was placed in a sterile container. The nasal half was placed in 10% formalin. The fixed specimen showed disorganization of the choroid and retina and elevation of the nerve head.

Microscopically, keratic precipitates were present on the corneal endothelium. The chamber angle was open, and the trabecular meshwork was filled with lymphocytes and plasma cells. These cells were also found about Schlemm's canal. A severe inflammatory reaction involved the uveal tract and retina. In addition to epithelioid and giant cells scattered throughout these structures, there were many lymphocytes, plasma cells, eosinophiles, and mast cells. An inflammatory exudate extended along the surface of the ciliary body and into the vitreous. A few pseudocysts containing spherical forms of Toxoplasma-like organisms were found in necrotic portions of the retina, and an occasional one, in the adjacent choroid. One of these is shown in Figure 3. The chorioretinal lesions were indistinguishable from those in cases of toxoplasmic chorioretinitis previously reported. There was edema of the nerve head and depression of the lamina cribrosa. The optic nerve was normal.

The diagnosis, on the basis of the histopathology, was toxoplasmic endophthalmitis.

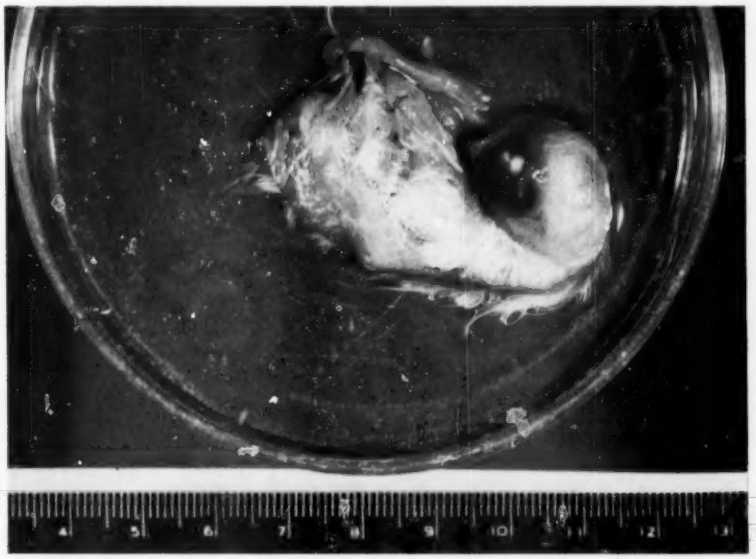

Fig. 3.—Toxoplasma in a pseudocyst in the retina. The parasites are partially obscured by pigment granules in an overlying macrophage.

COMMENT

The results reported above establish an unequivocal identification of T. gondii as the cause of the uveitis in this case.

The relatively low dye test titers found in the serum of this patient prior to enucleation support the idea expressed by Jacobs, Cook, and Wilder [12] that the diagnosis of ocular toxoplasmosis must be considered on a qualitative, rather than a quantitative, basis. A positive serological or skin test result appears to be of significance regardless of the height of the reaction. The rapid rise in titer of the patient's serum following enucleation may be explained on the assumption that some soluble antigen or some parasites were liberated from the globe as a result of the manipulations at the time of operation. The positive skin test prior to enucleation, the erratic

dye test titers, and the consistently negative complement fixation test found afterward rule out the possibility that by coincidence this was a case of recently acquired toxoplasmosis in which the antibodies were just being elaborated. The erratic changes in dye test titer are of particular interest in view of the report of Hogan, Thygeson, and Kimura [9] that rapid fluctuations in dye test antibody have been found in some of their cases of uveitis. Franceschetti and Bamatter [4] have also reported two cases in which fluctuations in dye test titer were obtained, and a few such cases have been observed also in a series of cases of uveitis in which we have performed repeated serological tests.†

Frenkel [5] (1948) reported that an anamnestic rise in dye test antibody followed skin testing. Vivell [16] (1952) similarly reported this finding in some of his cases. Such a rise in titer did not follow skin testing in the case reported here, at least not in the dye test one week following the intradermal injection. It may also be mentioned here that in 20 cases which we have studied in this regard no such rise in dye test titers was found following the intradermal test. Woods and associates [18] also reported no rise in serum antibody levels following the skin test.

It is believed that this case definitely establishes adult ocular toxoplasmosis as a disease entity. Despite the low dye test titer found in the serum of the mother of the patient, a result which, incidentally, could be expected in at least 50% of the general population in her age group (Feldman [3]), the absence of cerebral calcifications in the patient, the unilateral involvement, and the fact that no symptoms appeared until the approximate age of 22 make it appear unlikely that the eye lesions were the result of a congenital infection. With the increase of knowledge of the various systemic manifestations of adult acquired toxoplasmosis (Sexton, Eyles, and Dillman,[15] 1953; Feldman [3]), it is becoming apparent that there are no distinct differences between the adult and the neonatal form of the disease. The differences appear to be those of degree rather than of kind, and it seems best to discard the conceptual barrier erected earlier to distinguish congenital and acquired toxoplasmosis. The fact that cases of granulomatous uveitis suspected to be due to Toxoplasma are generally chronic in nature, and of long duration, suggests that ocular toxoplasmosis in adults becomes manifest long after the systemic manifestations have disappeared and when antibody titers have descended to relatively low levels.

From the standpoint of diagnosis, the low dye test results which were found in this case prior to enucleation indicate, as has already been mentioned, that toxoplasmosis need not be excluded from consideration merely because only a low level of antibody is found. However, the frequency of positive reactions in the dye test or skin test for toxoplasmosis in the general population makes the problem of diagnosis in the individual case still a matter of elimination. The only truly significant reaction may be a negative one, which rules toxoplasmosis out of consideration, but a positive reaction makes this infection only one of the possible etiologic factors to be considered. Possibly the most conclusive evidence of the toxoplasmic etiology of a case of uveitis may be fluctuations in dye test titer, but these, obviously, do not occur in every instance. Considerably more work will be required on the serology of Toxoplasma infections before we arrive at a definitive diagnostic method for associating this parasite with individual cases of ocular disease.

† Fair, J. R., and Jacobs, L., to be published.

SUMMARY

Parasites were isolated in mice, chick embryos, and roller tube cultures of chick and mouse embryo tissues after inoculation with the macerated inner layers of a human eye enucleated because of pain and blindness due to chorioretinitis of eight and one-half years' duration. By means of serological and cross-immunity tests, the identity of these parasites as Toxoplasma gondii was established. The dye test titer of the patient before enucleation was 1:64. After enucleation, weekly tests showed great variation, from 1:4,096 to 1:128. The significance of these findings is discussed.

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TOXIN-LIKE SUBSTANCE OF TRACHOMA VIRUS

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A SERIES of trustworthy investigations indicates that distribution of trachoma virus is confined to the epithelial layer of the conjunctiva.* Nevertheless, the significant clinical change in trachoma is subepithelial inflammation, e. g., follicle formation and cellular infiltration. In addition, in the acute stage of infection there is often the association of a preauricular adenopathy. Might these changes not be incurred by a toxin or toxin-like substance produced by the trachoma virus? On the other hand, a toxin or a similar factor has been demonstrated in related viruses, namely, the viruses of psittacosis and lymphogranuloma venereum. The problem as to whether trachoma virus produces a toxin or like substance may, therefore, be worthy of investigation.

DESIGN OF THE EXPERIMENT

Conjunctival matter from trachoma cases with a great number of inclusion bodies no doubt contains trachoma virus in high concentration. If a soluble toxin or toxin-like substance is being produced by the trachoma virus, an emulsion prepared from such material should be a solution of the toxin with corpuscular virus. If such emulsion is then filtrated through a gradocol membrane, which retains viral elements, the filtrate will be a toxin solution without causative virus.

The presence of the toxin in such a filtrate may be most sensitively demonstrated by means of inoculation of the human conjunctiva with the filtrate.

The only problem was how to obtain donors for such experiments. Although trachoma is prevalent in Japan, cases with innumerable inclusions are relatively rare. During the course of large-scale campaigns against trachoma with antibiotics, we have found a reasonable number of such cases during the past two years. These patients were used as the donors for the present study.

DONORS

Forty-one eyes of 26 patients with severe trachoma were made use of for obtaining the material. In 21 of these 26 patients, trachoma was in the early chronic stage, and inclusions were found in considerable number in the scrapings in each case. In the other five patients, the infection was in the acute stage, and a great number of inclusions was also shown in the scrapings. For the inoculation of the first volunteer, five eyes of three patients were utilized. For the second and the third volunteer, 21 eyes of 14 patients and 15 eyes of 9 patients were selected as donors, respectively.

Supported by the Scientific Research Grant from the Japanese Ministry of Education.
From the Department of Ophthalmology, Kumamoto University Medical School.
* References 1 to 3.

PREPARATION AND PURIFICATION OF TOXIN SOLUTION

For the inoculation of the first volunteer, the solution was prepared every other day from each of the five eyes, and each solution was used for two days' inoculation, except the last preparation, which was used for three days. For the preparation of the solution, the conjunctivae of both fornices were biopsied and gently ground with sand, sterile distilled water being added up to 4 cc. After centrifugation at 3,000 rpm for 15 minutes, the supernatant fluid was first filtrated, using a minute sand-pulp filter. The filtrate was then again filtered, under a combination of positive (50-60 mm. Hg) and negative (50-60 mm. Hg) pressure, through a gradocol membrane† of 50 mμ average pore size. About 2.0 cc. of final filtrate was thus obtained each time.

For the inoculation of the second volunteer, a similar technique was employed. To obtain more concentrated toxin solution, however, the following modification was made: Conjunctivae of two to four eyes were used at each preparation of the solution, and, at the suggestion of Dr. K. F. Meyer, of the University of California, the preliminary filtration through the sand-pulp filter was omitted.

The third inoculation was designed to determine the thermostability of trachoma toxin. The conjunctival emulsion was, therefore, first heated at 100 C. for five minutes. After centrifugation, the supernatant fluid was used as the inoculum without being filtrated, as the virus had certainly been killed by the heating.

INOCULATION OF MICE

About 1 cc. of the fluid was left unfiltrated with each final filtration through gradocol membrane. This unfiltrated sample, which contains virus, and, if present, toxin, was injected intravenously into a white adult mouse each time. In no case was any toxic manifestation brought about in the mouse.

INOCULATION OF HUMAN VOLUNTEERS

CASE 1.—A 12-year-old boy. The conjunctivae were normal. Examination of scrapings revealed normal epithelium, with essentially negative cytologic and bacteriologic findings. A culture was positive for a small number of staphylococcic colonies.

Inoculation.—A small drop of the ultrafiltrate was instilled into the left eye of the volunteer. The inoculation was repeated every half-hour or every hour during the day and less frequently during the night.

No reaction was observed in the conjunctival sac for the first six days. On the seventh day, however, a number of translucent follicles, arranged in a row, appeared in the deep border of the lower fornix. There were no inflammatory signs, such as hyperemia or discharge, however; the condition looked like a "folliculosis." From this day on, however, the follicles increased in number, occurring in rows; in addition, inflammatory signs gradually appeared. Thus, on the 10th day, the appearance was that of follicular conjunctivitis with a scanty mucopurulent discharge. On the 11th day, the appearance was mild, but characteristic for an acute follicular conjunctivitis, as seen in the acute stage of trachoma infection. There was a considerable amount of mucopurulent discharge. Examination of a smear revealed polymorphonuclear cells 3+; monocytes, 1+; fibrin, 3+, and a small number of xerotic bacilli. A culture was negative for any pathogenic micro-organism. Examination of scrapings revealed epithelial cells of relatively normal appearance and no inclusions. Preauricular adenopathy was not demonstrated. To our regret, further instillation was impossible, as the material had been consumed. Upon discontinuation of the instillation, the symptoms began to subside rapidly. The inflammatory signs disappeared within a few days. On the 22d day the appearance was that of a slight folliculosis. Examination on the 30th day gave no sign of folliculosis.

CASE 2.—This experiment was performed after a careful preparation, and one of us (J. H.) desired to be the subject of the experiment. He had never had any ocular inflammations, and his conjunctivae and corneae were proved to be normal by clinical examination, as well as by examination of scrapings and culture.

† Supplied by Dr. S. Arakawa, Institute for Infectious Diseases, Tokyo, Japan.

Inoculation.—For one week prior to the inoculation, as well as during the experiment, he was isolated from contact with patients. The inoculation was performed in his left eye in a manner similar to that in the first case. However, more frequent and more regular instillation was possible, during the night in particular, than in the previous case, and the instillation could be continued as long as 15 days, owing to his devoted cooperation and to a sufficient supply of the material. The right eye served as the control, receiving instillations of a control solution. The control solution was prepared in a manner similar to the original inoculum without the use of conjunctival material. Thus, the effect of the extract from sand, gradocol membrane, and other agents was excluded.

No reaction was observed in the conjunctival sac for the first four days after the beginning of the instillation. On the fifth day, however, there was a slight secretion and a slight capillary injection of the tarsal conjunctiva of the left eye. On the next day, there was diffuse hyperemia and slight edema of the conjunctival sac. The smear of the discharge revealed fibrin 3+, polymorphonuclear leucocytes 3+, and monocytes 1+. There was a small number of Neisseria catarrhalis organisms in the smear and culture. From the seventh day, therefore, a 0.5% solution

Clinical finding (Case 2) after 11 days' instillation of virus-free ultrafiltrate of trachomatous material (left eye). (Upper) The lid is swollen and ptosed. (Lower) The conjunctival sac is acutely inflamed, with follicular hypertrophy.

of streptomycin was instilled to eliminate bacterial contamination until a negative bacteriology resulted, namely, 10 times a day for two days. To exclude the possibility of an allergic reaction to streptomycin, the antibiotic was used in both eyes in the same manner. On the eighth day there was considerable hyperemia and cloudiness in the conjunctivae, as well as in the semilunar fold of the left eye. The bulbar conjunctiva was also reddened, and there was a considerable amount of discharge. He complained of discomfort in the eye, but there was no reaction in the control eye. On the 11th day there was swelling and tenderness of the preauricular lymph node in the left side and follicular hypertrophy of the conjunctivae of the fornices. There was injection and slight swelling of the capillary loop at the upper limbus, but no pannus formation. The lids looked edematous, and there was slight ptosis. The symptoms increased steadily thereafter, and on the 14th day the appearance was typical of trachoma in its acute stage. Nevertheless, repeated scrapings on the 11th, 14th, and 19th days were negative for inclusions, and the epithelial changes in the scrapings were very slight.

On the 14th day the discharge from the left eye was transferred to his right eye, which looked normal, as well as to one eye of another volunteer. In both these eyes, however, no inflammation was brought about until the end of the experiment.

By the evening of the 15th day the instillation was stopped. Discontinuation was followed by prompt improvement, but the improvement was slower than in the first case, and it took one and three weeks respectively for the acute sign and the follicle formation to disappear completely.

CASE 3.—A 11-year-old boy. The conjunctivae were normal on clinical, cytological, and bacteriological examinations. The heat-killed material, prepared every three days, was instilled into the boy's left eye in a manner similar to that in the previous cases. The instillation was continued for 20 days. No obvious inflammation was brought about in his eye throughout the whole course of the experiment. A scanty secretion was observed for a few days during the instillation, but the discharge contained only a small number of cellular elements and fibrin was absent in the discharge. By the end of the instillation there appeared a few tiny follicular swellings in the lower fornix, which disappeared 10 days after the cessation of the instillation.

INTRACUTANEOUS REACTION WITH TRACHOMA ANTIGEN AS A COMPLEMENTARY EXPERIMENT

From three eyes with typical trachoma with a large number of inclusions, other than the eyes used in the previous experiment, specimens of conjunctiva were taken for biopsy. An emulsion of the conjunctiva prepared similarly to that in the previous experiment was centrifuged at 3,000 rpm for 30 minutes. The supernatant fluid, which contained virus and toxin, was used as the antigen. The precaution against bacterial contamination was a frequent application of a solution of penicillin (1 mg. per cubic centimeter) and streptomycin (5 mg. per cubic centimeter) in the donor's conjunctiva for three days prior to the removal.

Three patients with acute trachoma, six with typical chronic trachoma, and seven normal school children were selected as the subjects. In the selection of normal cases, care was taken to examine the cornea by slit lamp. If there were any doubtful changes at the upper limbus, the case was discarded.

In these 16 cases, the antigen was injected intracutaneously in the same manner as in the tuberculin test, along with an injection of control solution. Examinations after 24 and 48 hours revealed that in some cases there was a relatively large area of redness of the skin (the maximum was 30 by 50 mm.) but no induration. In others there was no reaction at all. In the positive cases, the reaction disappeared in a course of 48 to 72 hours. The positivity was, however, irregular and it did not seem to have any relation to trachoma infection.

COMMENT

A toxin or similar factor has been demonstrated in related viruses, such as the viruses of psittacosis and lymphogranuloma venereum. The toxin from these viruses kills young mice after intravenous injection. However, this toxin is labile, is not readily separated from the elementary bodies, and is readily inactivated at room temperature.[4]

Since the trachoma virus has not yet been cultivated to any extent, attempts to demonstrate production of a toxin from trachoma virus cannot be performed on a large scale. Our present experiment in the first two cases of human volunteers suggests, however, that there is a toxin or similar substance of trachoma virus which causes trachomatous inflammation. This substance, if produced by elementary bodies, seems to be separated from the virus and to be rather stable. It maintains its potency in a refrigerator for a few days at least. It is not known whether this substance would kill mice or not when used in a large dose. But it is certain that a repeated instillation of the substance is capable of causing noncontagious, trachoma-like inflammation in the human conjunctiva. The results may give credence to the view that the primary change of trachoma is that in the epithelial layer of the conjunctiva, and that subepithelial changes and preauricular adenopathy are secondary to it, the result of a toxin from the virus in the epithelium.[5]

However, the experiment on the third volunteer suggests that the toxin is mostly, if not entirely, destroyed by heat. Further, the complementary experiment suggests that the toxin, as well as other antigens which may be contained by the virus, does not seem to give a cutaneous reaction of diagnostic value.

SUMMARY

A virus-free ultrafiltrate of trachomatous material was repeatedly introduced into the conjunctiva of two human volunteers, as the result of which an acute follicular conjunctivitis, similar to trachoma in its acute stage, and, in one of the cases, a preauricular adenopathy were brought about. It suggests strongly that a toxin or toxin-like substance is produced by trachoma virus.

A preliminary note of this paper containing the results in the first volunteer was mimeographed and distributed by the World Health Organization as Doc. WHO/Trachoma/21, on Oct. 22, 1951.

Kumamoto University Medical School, Honjo-Machi.

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INFLUENCE OF LOW-VOLTAGE X-RADIATION ON INHIBITION AND PREVENTION OF NEW VESSELS IN CORNEA

Comparison with Influence of Cortisone

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WHEN IT is desirable to limit the amount of vascularization in the cornea, the clinician usually resorts to the use of low-voltage x-rays, cortisone, or beta radiation. Although low-voltage x-rays are used in this way rather extensively, there are few reports on experimental work which should form the basis of a procedure difficult to assess clinically. While it has been shown that large doses of x-rays produce corneal damage followed by vascularization (Rohrschneider, 1929; Martin and Reese, 1942), in a series of experimental studies using total doses as low as 1,500 r Scheie and his collaborators have concluded that the vascularization produced by intracorneal sodium hydroxide injection can be markedly inhibited by low-voltage x-rays (1950). They found that daily exposures were more effective in inhibiting corneal vascularization than exposures given at longer intervals and that small single doses, of 300 r, were as effective as larger ones, up to 1,000 r. A definite effect could be seen only at the end of the first week, by which time presumably a total of 1,800 r had been given.

The first purpose of the present report is to add to the little experimental work that has been done in investigating the effect of low-voltage x-rays in reducing new-vessel formation in the cornea and to use a method of measuring corneal vascularization which is possibly an improvement on that hitherto used in these experiments. Both inhibition and prevention of new-vessel growth into the cornea as they are influenced by x-irradiation will be studied.

The second purpose is a comparison of the effects on corneal vessels of low-voltage x-radiation and of cortisone applied topically. It has already been shown experimentally that cortisone given topically as a subconjunctival injection or as drops may inhibit the growth of new vessels (Jones and Meyer, 1950; Ashton, Cook, and Langham, 1951; Lister and Greaves, 1951, and Michaelson, 1952).

MATERIAL AND METHODS

Low-Voltage X-Radiation Experiments.—The method of producing and measuring corneal vascularization has already been described (Campbell and Michaelson, 1948). A standard thermal lesion was produced in both corneas of 45 rabbits of about 1.5 kg. weight. The lesion was made by means of an electrocautery applied about 2.5 mm. from the limbus in the 12 o'clock

meridian. An attempt to standardize the lesion was made by supplying the cautery with a fixed voltage and applying it for a fixed time. The cautery was reapplied to the wound daily for a certain number of days during the course of each experiment.

With the aid of a Philips low-voltage contact therapy machine, using 50 kv. and 2 ma., x-rays were applied to the upper portion of the cornea of the right eyes of all the animals, the area irradiated extending from the wound to the limbus and therefore including the vascularized portion of the cornea and the limbal vessel from which they budded. Exposure was given through a 15 mm. aperture.

In one series of experiments (inhibition experiment) the radiation was applied daily during the six days of cauterization, a total of 1,800 r being given to each right eye. The animals were injected on the eighth day of the experiment.

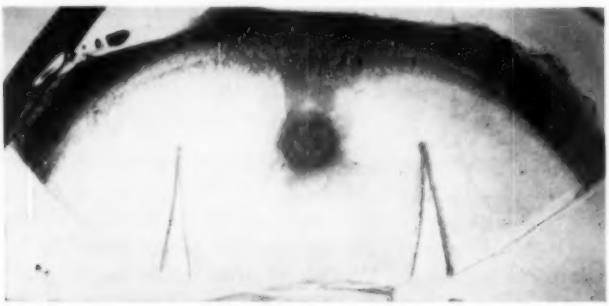


Fig. 1.—Injected vascular area in left (control) eye of Rabbit 138 (Table 1). The vascular triangle is well developed.

Fig. 2.—The injected vascular area in the right (irradiated) eye of Rabbit 138 (Table 1). The vascular triangle is inhibited.

In the second series of experiments (prevention experiments) an endeavor was made to assess the capacity of the radiation to diminish new-vessel formation taking place as the result of previous irradiation. In these experiments there were two main groups: one, in which the radiation was given some time prior to the onset of new-vessel formation, and the other, in which the radiation was given during the first few days of the beginning growth, the vessel-producing influence (the ulcer) continuing to be active after the irradiation had ceased. The latter group was again subdivided according to changes in dose and time factors.

Cortisone Experiments.—These have already been reported (Michaelson, 1952). In these experiments a standard lesion was produced in both corneas of rabbits, as described above, and this lesion was maintained by serial cauterization for 10 days. During these 10 days, 1.25 mg. of cortisone was injected subconjunctivally every third day into the right eyes. At the end of the period these animals were killed and the areas of vascularization demarcated and measured,

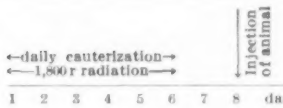
using the method described above. The experiments were thus an assessment of the capacity of cortisone to inhibit vessel growth. No prevention experiments were made, as it was not considered likely that the influence of cortisone would continue after the cortisone had disappeared from the tissues.

Cultures of material from the conjunctiva were made from each animal during these experiments. They were sterile.

RESULTS

Radiation Experiment (Inhibition).—With each animal a satisfactory injection was obtained. Figures 1 and 2 illustrate the appearance of the triangular areas of vascularization, Figure 1 being from the left (control) eye of Rabbit 138, while Figure 2 is from the right (irradiated) eye of the same animal. In all animals there was a striking difference between the vascular areas in the right and left eyes. The

TABLE 1.—*Areas of Vascularization in Inhibition Experiment* *



Rabbit No.	Left Eyes (Not Irradiated)		Right Eyes (Irradiated)	
	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.
137	2.4	7.6	2.2	1.5
138	2.6	8.1	2.1	2.8
139	2.3	9.0	2.6	2.6
140	3.2	4.2	2.5	2.8
141	2.6	5.1	2.1	2.4
142	2.5	6.7	2.1	2.7
143	...	6.2	...	1.1
144	2.5	4.1	2.5	0.5
145	3.3	7.0	2.5	1.2
146	2.5	5.3	2.1	1.1
147	2.3	4.5	2.5	1.0
148	2.5	9.1	2.9	1.1
151	2.9	9.4	2.5	1.1

* A total of 1,800 r, given in six divided doses, for six days.

results are given in Table 1. The extent of vascularization is calculated from the base and height of the vascular triangular areas.

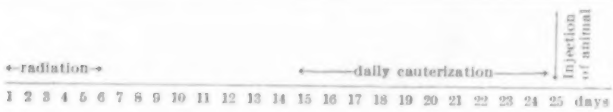
The wounds were all between 1.25 and 1.75 mm. in diameter. The mean of the wound-limbus distances in the left eyes was 2.4 mm. (range, 2.3 to 3.2 mm.); the mean of the wound-limbus distances in the right eyes was 2.4 mm. (range, 2.0 to 2.9 mm.). The similarities of wound-limbus distances and wound diameters permit comparison of the right and the left eyes with regard to the area of vascularization produced.

The mean of the vascular areas in the left eyes was 6.8 sq. mm. (range, 4.1 to 9.4 sq. mm.); the mean of the vascular areas in the right eyes was 1.7 sq. mm. (range, 0.5 to 2.8 sq. mm.). There was a significant difference between the two eyes. A total of 1,800 r of low-voltage x-radiation in daily doses of 300 r has a considerable influence in inhibiting new-vessel growth in the cornea. From the experiments described, it seems capable of reducing the expected vascularization by 75%.

Radiation Experiment (Prevention).—The prevention experiments detailed in Tables 2, 3, 4, and 5 were of two kinds. In the experiment detailed in Table 2 the radiation was given 14 days before the lesion and the vascularization were initiated, while in the experiments detailed in Tables 3, 4, and 5 the radiation was applied during the first few days of the beginning vascularization, the lesion thereafter continuing to be active and to provoke fresh vascularization. The experiments detailed in Tables 3, 4, and 5 differed from one another in respect to the dose of radiation and the times given for the radiation to exercise its possible influence. These differences are indicated in the diagrams at the head of each T[illegible].

The mean of wound-limbus distances in the left eyes w[illegible] 2.4 mm. (range, 2.0 to 2.8 mm.); the mean of wound-limbus distances in the right eyes was 2.2 mm.

TABLE 2.—*Radiation Experiment (Prevention)* *



Rabbit No.	Left Eyes (Not Irradiated)		Right Eyes (Irradiated)	
	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.
47	2.3	3.6	2.1	3.8
48	2.6	9.4	2.0	7.7
49	2.3	3.3	2.0	7.7
50	2.8	9.5	2.0	8.1
51	2.5	3.8	2.3	6.8
52	2.5	10.0	2.5	7.5
53	2.5	6.6	2.1	6.8
54	2.0	7.9	2.0	8.8
55	2.4	10.3	2.5	7.9
56	2.5	7.7	2.0	11.6

* 1,500 r, given in three divided doses.

(range, 2.0 to 2.5 mm.). The wound diameters were all between 1.25 and 1.75 mm. The similarity of wound-limbus distance and wound diameter permits of comparison of the right and left eyes with regard to the areas of vascularization produced.

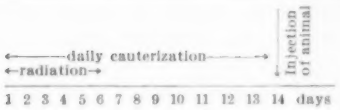
The mean of the vascular areas in the left eyes was 7.1 sq. mm. (range, 3.3 to 10.0 sq. mm.); the mean of vascular areas in the right eyes was 7.7 sq. mm. (range, 3.8 to 11.6 sq. mm.). There is no significant difference between the areas of vascularization produced in the treated and the untreated eyes.

The wound diameters were all between 1.25 and 1.75 mm. The mean of wound-limbus distances in the left eyes was 2.3 mm. (range, 2.0 to 2.6 mm.); the mean of wound-limbus distances in the right eyes was 2.3 mm. (range, 2.0 to 2.8 mm.). The similarity of wound-limbus distance and wound diameter permits of comparison of the right and left eyes with regard to the areas of vascularization produced.

The right eye of Animal 22 had a vascular area of 1.6 sq. mm. In view of the great discrepancy between this and the other areas measured, this figure has been removed from the calculations.

The mean of the vascular areas in the left eyes was 8.5 sq. mm. (range, 4.0 to 12.4 sq. mm.); the mean of vascular areas in the right eyes was 8.5 sq. mm. (range, 4.1 to 11.3 sq. mm.). There is no significant difference between the areas of vascularization produced in the treated and the untreated eyes.

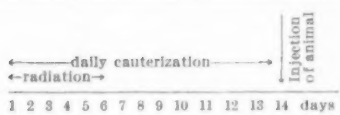
TABLE 3.—*Radiation Experiment (Prevention)* *



Rabbit No.	Left Eyes (Not Irradiated)		Right Eyes (Irradiated)	
	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.
22	2.3	9.1	2.3	1.6
23	2.5	7.9	2.5	9.5
25	2.0	12.4	2.0	11.3
26	2.0	10.5	2.0	11.3
159	2.0	4.0	2.0	6.2
160	2.5	9.2	2.4	4.1
161	2.5	8.8	2.5	8.1
162	2.6	7.6	2.4	6.0
165	2.5	8.2	2.8	11.3

* 1,500 r given in six divided doses.

TABLE 4.—*Radiation Experiment (Prevention)* *



Rabbit No.	Left Eyes (Not Irradiated)		Right Eyes (Irradiated)	
	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.
27	2.3	6.3	2.3	6.0
28	2.2	8.0	2.3	4.9
29	2.3	7.5	2.0	6.0
30	2.0	9.5	2.0	8.5
31	2.5	8.5	2.0	8.0
33	2.7	7.0	2.5	6.3
34	2.5	9.4	2.0	10.0

* 1,500 r given in three divided doses.

The wound diameters were all between 1.25 and 1.75 mm. The mean of wound-limbus distances in the left eyes was 2.4 mm. (range, 2.0 to 2.7 mm.); the mean of wound-limbus distances in the right eyes was 2.4 mm. (range, 2.0 to 2.5 mm.). The similarity of wound-limbus distance and wound size permits of comparison of the right and left eyes with regard to the areas of vascularization produced.

The mean of vascular areas in the left eyes was 7.3 sq. mm. (range, 6.8 to 8.0 sq. mm.); the mean of vascular areas in the right eyes was 7.1 sq. mm. (range, 4.9 to 10.0 sq. mm.). There is no significant difference between the areas of vascularization produced in treated and in untreated eyes.

The wound diameters were all between 1.25 and 1.75 mm. The mean of wound-limbus distances in the left eyes was 2.0 mm. (range, 1.8 to 2.1 mm.); the mean of wound-limbus distances in the right eyes was 2.0 mm. (range, 1.8 to 2.1 mm.). The similarity of wound-limbus distance and wound size permits of comparison of the right and left eyes with regard to the areas of vascularization produced. The mean of vascular areas in the left eyes was 12.2 sq. mm. (range, 10.7 to 13.1 sq. mm.); the mean of vascular areas in the right eyes was 13.5 sq. mm. (range, 12.4 to 17.1 sq. mm.). There is no significant difference between the areas of vascularization produced in the treated and the untreated eyes. The results of the experiments detailed in Tables 2, 3, 4, and 5 indicate that x-irradiation does not appear to have

TABLE 5.—*Radiation Experiment (Prevention)* *

Rabbit No.	Left Eyes (Not Irradiated)		Right Eyes (Irradiated)	
	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.	Wound-Limbus Distance, Mm.	Area of Vascularization, Sq. Mm.
15	2.0	12.7	2.0	13.2
16	2.0	10.7	2.0	12.4
17	2.0	13.1	2.0	12.7
18	2.1	11.2	2.1	12.6
19	2.0	13.1	2.0	13.1
20	2.0	12.4	1.8	17.1

* 1,500 r given in three divided doses.

any influence in preventing new-vessel formation in the cornea either when given before the onset of the vessel formation or early in its development.

Cortisone Experiments (Inhibition).—These experiments have already been reported (Michaelson,[4] 1952). In that report it was shown that the effect of the cortisone in reducing the area of vascularization is dependent on the distance of the ulcer from the limbus; the farther the ulcer which provokes the new-vessel growth is from the limbus, the greater is the effect of cortisone in reducing the area of vascularization. In the radiation inhibition experiment (Table 1), the range of ulcer-limbus distance was 2.1 to 3.3 mm. For the purpose of a strict comparison of the results of radiation inhibition and those of cortisone inhibition, it is possible to consider only those animals of the cortisone inhibition experiment in which the ulcer was 2.1 to 3.3 mm. from the limbus. The reported results in these animals are tabulated as follows:

Wound-Limbus Distance, Mm.	Mean Area in Untreated Eyes, Sq. Mm.	Mean Area in Treated Eyes, Sq. Mm.	Diminution of the Area %
2.1-2.9	4.8	1.7	65
3.0 or more	4.3	1.5	65

All animals in which the wound-limbus distances were 2.0 mm. or less have been omitted from consideration. These results indicate that cortisone can reduce expected vascularization by 65% if the standard lesion causing the vascularization is situated between 2.1 and 3.0 mm. or more from the limbus. This degree of inhibition of vascularization is very similar to that reported after x-irradiation (75%).

COMMENT

Comment might be made on the duration of the radiation experiments and the dose of radiation used.

The duration of the experiments was determined in the first place by the time necessary to permit the effect of radiation on the vessels to be manifested. The inhibition experiment clearly shows that this effect can be manifested within a few days. As the prevention experiments failed to show any influence of x-irradiation, the radiation was given a longer time in which to exert a possible influence on the vessels. Thus, in the prevention experiments shown in Tables 2 and 5, periods of 25 and 21 days, respectively, were allowed to elapse between the onset of the radiation treatment and the death of the animal. These times were probably sufficiently long to permit of the radiation causing some prevention if it were capable of doing so. The observation time was also compatible with the time available for effective treatment in certain clinical conditions, for example, the attempted inhibition of new-vessel growth into the cornea following a corneal graft operation.

The dose used was such as to be less than the amount which might possibly damage the eye and such as to be comparable to the amount commonly used in clinical practice. In keeping with the findings of Scheie and his co-workers (1950), no noticeable damage was done to the eyes in these experiments as the result of the radiation used. Moreover, these experimenters were convinced that a dose of 300 r was as effective as one of 1,000 r in inhibiting the extent of corneal vascularization.

In assessing results, the extent of vessel growth into the cornea was taken as the criterion because it could be accurately measured. The width of the vessels and the density of the vascularization were ignored because of the great difficulty in assessing them.

If the duration of the experiments, the doses of radiation used, and the mode of measuring the vascularization be accepted as valid for our purpose, it is to be concluded that low-voltage x-irradiation has a profound effect in inhibiting new-vessel growth, reducing the anticipated growth by 75%. It is to be noted that this reduction refers to conditions in which the lesion is placed 2.1 to 3.3 mm. from the limbus. The radiation does not, however, prevent the growth of new vessels when the radiation is given in anticipation of their commencement or of their continued development.

The cortisone inhibition experiment shows that for similar conditions, that is, for similar wounds placed 2.1 to 3.0 mm. or more from the limbus, the reduction of vascular area resulting from the use of cortisone is practically the same as that resulting from the use of radiation.

SUMMARY AND CONCLUSIONS

In 45 rabbits standard thermal lesions were produced in both corneas. The effect of low-voltage x-irradiation on the resulting vascularization in the right eyes was studied, the left eyes being used as controls.

The radiation was given at such times relative to the onset and growth of the new vessels as would give indication to the effect of the radiation on inhibition of new-vessel formation.

The radiation was given at such times relative to the onset and growth of the new vessels as would give indication of the effect of the radiation on prevention of new-vessel formation.

The doses of radiation used and the durations of the experiments were probably sufficient, and to some extent were determined by their clinical applicability in man.

Mention is made of the influence of cortisone applied topically in inhibiting new-vessel formation in the cornea. The figures are taken from a report previously published by one of us, care being taken to use only such as were obtained from experiments in which the wound-limbus distances were comparable to those in the radiation inhibition experiment reported here.

The radiation was effective in inhibiting new-vessel growth into the cornea. Seventy-five per cent of the expected vascularization was inhibited.

The radiation was ineffective in preventing new-vessel growth into the cornea.

Cortisone was effective in inhibiting new-vessel growth into the cornea to the extent of 65% of the expected vascularization.

Radiation and cortisone in the doses usually used clinically are almost equally effective in inhibiting new-vessel growth into the cornea.

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Miss Eva Lewkowitz gave technical assistance.

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REMOVAL RATE OF RADIOSODIUM (Na^{24}) FROM HUMAN ORBIT IN GRAVES'S DISEASE AND IN HEALTH

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THE MECHANISMS responsible for the production and maintenance of the ocular complications of hyperthyroidism have not been entirely elucidated. Accordingly, the rate of removal of radioactive sodium from the orbits of healthy human subjects and of patients with the mild and severe extremes of ophthalmopathy has been observed with a view toward determining whether venous obstruction or active inflammation accounts for the phenomena. The extremes of the eye changes have been variously termed "thyrotoxic" and "thyrotropic," or "simple" and "malignant" exophthalmos, among other names, but in this paper they will be called "mild" and "severe."

It has been recognized that orbital tension is increased in the severe form of thyroid ophthalmopathy. Quantitative measurements reveal an increase proportionate to the degree of exophthalmos.[1] Rundle and Pochin [2] have shown also that there is a significant increase in orbital bulk which tends to correlate quantitatively with the degree of exophthalmos. This led Pochin [3] to postulate, at least in the less severe forms of ophthalmopathy, that as the orbital tissue bulk is increased a stage of severity is reached at which vascular drainage is mechanically impeded. The obstruction then produces edema, severe protrusion of the globe, and, later, fibrosis of the intraorbital structures.

Edema, however, can result from increased capillary permeability and arteriolar dilatation (active hyperemia), as well as from venous obstruction (passive congestion). Inasmuch as the rate of removal of Na^{24} from the orbit might distinguish between the two vascular conditions, a method using radiosodium, Na^{24}, was devised for measuring this disappearance rate and the present study carried out.

METHODS

Measurements of radioactivity were made by a Geiger-Müller counter shielded with ½ in. (13 mm.) of lead except for a window 7 by 3 cm. With the patient in the supine position, the counter was so positioned at the lateral aspect of the orbit that the center of the window was approximately over the site where the tip of the needle used for injection was to reach. A background count was determined for a period of five minutes. After this, Na^{24} was inserted into the orbit by either of two methods, one of which was abandoned early, after it had proved relatively

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unsatisfactory. The other was employed throughout the remainder of the study. The Na^{24} in the first experiments was placed in the orbit by a retrobulbar injection through the lower lid into the retrobulbar muscle cone with the same technique as is commonly employed to produce local surgical anesthesia with procaine. The rate of disappearance of the Na^{24} was then determined. This was the procedure which was discarded.

TABLE 1.—*Removal Times for Na^{24} After Retrobulbar Injection*

Type of Eye Change	Subject	Eye	Exophthalmos, Mm.	Time to Reduce Initial Count, Min.				B. M. R.	Duration of Ocular Signs, Mo.
				1/2	1/4	1/6	1/8		
Mild	O. C.	O. D.	17.0	13	27	35	45	+51	12
	G. L.	O. D.	14.5	7	15	20	23	+46	1.5
	A. M.	O. S.	16.0	16	44	57	67	+41	6
	A. E.	O. D.	19.0	13	26	51	60	+21	1.5
	A. E.	O. S.	19.0	9	23	32	40	+21	1.5
	L. M.	O. D.	23.0	13	46	68	85	+11	48
	J. S.	O. D.	19.5	10	18	24+	..	−15	2
	J. S.	O. D.	20.5	25	66	99+	..	−17	7
Severe	F. N.	O. D.	20.5	12	16	18	19	+57	9
	D. O.	O. D.	22.0	9	16	20	24	+32	10
	M. B.	O. D.	20.5	23	50	64	75	+30	5
	M. M.	O. S.	18.0	11	20	27	34	+30	36
	C. C.	O. S.	15.0	25	28	36	42	+26	7
	C. C.	O. S.	17.5	7	15	19	26	+18	9
	C. C.	O. D.	16.0	7	15	19	24+	+ 9	2
	M. F.	O. D.	27.0	16	24+	..	..	− 7	24
	R. R.	O. S.	21.5	41	71	83	..	− 9	8
	C. A.	O. D.	23.0	9	20	29	..	−24	7

TABLE 2.—*Removal Times for Na^{24} After Injections into Intraorbital Fat*

Type of Eye Change	Subject	Eye	Exophthalmos, Mm.	Time to Reduce Initial Count, Min.				B. M. R.	Duration of Ocular Signs, Mo.
				1/2	1/4	1/6	1/8		
Mild	A. C.	O. D.	21.0	7	15	18	24	+40	6
	M. B.	O. D.	16.0	7	13	18	24	+33	3
	D. L.	O. D.	18.5	8	14	17	21	+30	7
	C. M.	O. D.	14.5	4	10	16	20	+28	8
	J. R.	O. D.	22.0	7	13	17	22	+ 1	½
	J. S.	O. S.	25.5	10	19	26	32	± 0	24
	L. F.	O. D.	32.0	10	24	34	43	− 2	300
	A. M.	O. D.	25.5	9	18	22	27	− 8	42
	B. M.	O. D.	24.0	16	30	40+	..	−17	130
Severe	V. S.	O. D.	17.0	8	18	30	39	+63	11
	A. L.	O. D.	22.0	9	22	28	34	+48	6
	M. S.	O. S.	27.0	20	40	42+	..	+37	30
	C. C.	O. S.	17.5	6	9	13	16	+14	3
	V. J.	O. S.	31.0	10	19	25	32	+ 7	8
	C. C.	O. S.	17.5	10	15	18	20	+ 5	4
	C. C.	O. S.	17.5	8	16	22	27	+ 5	4
	P. S.	O. S.	27.0	13	24	33	39	± 0	2
	E. H.	O. D.	29.0	12	27	35	34	− 3	1
	W. S.	O. D.	28.0	12	26	44	50	− 6	12

Subsequent injections were made with a 1.5 cm., 27-gauge needle through the skin and orbital septum, just superior to the lower temporal aspect of the bony orbital margin. With this technique it was assumed that all injections would be made into the orbital fat. The injection caused little discomfort, and local anesthesia was not needed. The dose of Na^{24} used throughout the work was 4 μc in 0.4 cc. of saline.

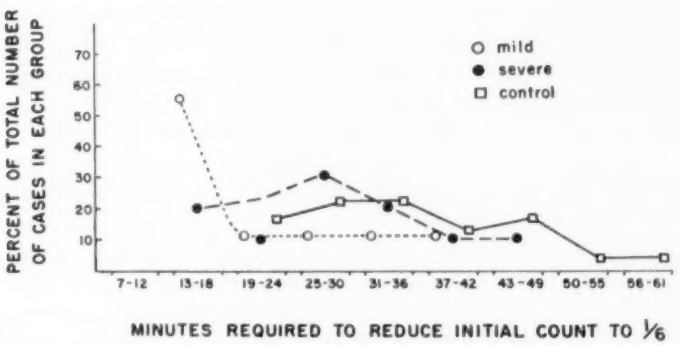
The patients were in three categories: those with the mild form of thyroid ophthalmopathy; those with the severe form of ophthalmopathy, and euthyroid controls, without clinical evidence of thyroid disease and with apparently normal orbits.

RESULTS

A. The first experiments were made on 14 patients, 7 men and 7 women, in whom 18 injections were made into the retrobulbar muscle cone. The ages ranged from 22 to 58 years. Of these patients, eight were definitely hyperthyroid and six

TABLE 3.—*Control Removal Times for Na^{24} After Injections into Intraorbital Fat*

	Minutes Required to Reduce Initial Count					Minutes Required to Reduce Initial Count			
Subject	½	¼	⅙	⅛	Subject	½	¼	⅙	⅛
R. W.	9	19	28	31	E. I.	8	16	23	27
A. E.	15	32	43	44+	H. B.	15	26	34	..
L. J.	10	20	28	30	M. B.	10	18	27	32
B. W.	12	19	24	27	J. R.	15	32	42	52+
G. L.	9	21	27	31	E. S.	14	24	44	53+
R. D.	21	53+	..	..	B. L.	15	32	47	57
R. L.	11	23	33	40	O. K.	13	27	38	48
M. K.	13	31	43	51	E. F.	16	40	52+	..
F. D.	6	19	25	31	J. I.	12	24	35	41
A. D.	9	18	24	30	J. D.	12	24	36	47
J. M.	13	27	37	44	M. E.	9	16	21	26
A. C.	8	23	33	45					



Removal rates in mild, severe, and control groups following Na^{24} injections into orbital fat. As the data are more complete, the time required to reduce the initial count to one-sixth is used in this graph. Elsewhere, in the text, the time required to reduce it to one-eighth is employed, but this in no way alters the results.

were considered euthyroid or hypothyroid despite the eye changes. Severe eye lesions were present in eight, and mild lesions in six.

It is apparent that the results were extremely variable, although no evidence of delay in removal was demonstrated (Table 1). It is known that the rate of disappearance of Na^{24} varies with different tissues,[4] and it could not be definitely determined whether the Na^{24} was being placed into muscle or fat, or possibly intravascularly. The technique was therefore not pursued further.

B. Nineteen injections on 17 patients were made through the lower orbital septum into the orbital fat. Of these, 5 were men and 12 were women. Their ages ranged from 21 to 67 years, and nine had the mild form, and eight the severe form, of ophthalmopathy. Eight of the 17 patients were clinically hyperthyroid, while 9 were euthyroid or hypothyroid. Twenty-three control subjects received one injection each. The results are summarized in Tables 2 and 3.

It is immediately apparent with this procedure, as with the injections into the retrobulbar muscle cone, that there is a wide variation in the rate of Na^{24} removal. Among the 23 control subjects the time required to reduce the orbital content of Na^{24} to one-eighth the initial concentration varied from 26 minutes to well over 1 hour, with a rough average of 42 minutes. In mild ophthalmopathy the range was from 20 to over 43 minutes, with an approximate mean of 30 minutes. The range in the severe form of eye disorder was from 16 to 50 minutes, with an approximate mean of 34 minutes. In the mild and in the severe ophthalmopathic groups there are several removal rates which are more rapid than any in the control series. Delay in removal rate beyond the slowest values in normals was not seen in any of the patients with severe or mild ophthalmopathy (Chart).

COMMENT

The nature of this study is essentially qualitative, rather than quantitative. The number of variables which might conceivably affect tissue-blood electrolyte equilibrium in human subjects is large. The exact position of the injection, anatomical variations, local fat content, cardiac function, local blood flow, age, emotional response to injection, duration of orbital disease, and degree of hyperthyroidism are some of the factors which might have a bearing on the removal rate of sodium from a local depot. Not all these factors were, or could be, evaluated. Nevertheless, there appears to be a time range within which the removal of injected Na^{24} is normally accomplished. No normal value was less than 26 minutes for removal of seven-eighths of the activity. Several values exceeded one hour required to accomplish the same result, but this upper limit was not defined. The rates in disease are seen to fall into approximately the same range.

The separation of the patients into categories termed respectively mild and severe ophthalmopathy is a clinical one and is a source of inaccuracy. The division is arbitrary because the two conditions overlap; in fact, they are thought by most to represent but two extremes of one disease process. The results of the present study lend some support to a unitarian concept. The rate of Na^{24} removal is perhaps significantly accelerated in the mild group and normal in the severe group. However, if the patients are classified according to duration of disease, there is a suggestive gradation in removal rate according to duration of ocular signs rather than type of disease, although the series is too small on which to base any definite conclusions (Table 4).

The removal rate from the orbit of Na^{24}, in the instances in which it is increased, may also reflect the extent of elevation of the metabolic rate. The instances in which there is rapid removal of the Na^{24} can be explained by the more rapid blood flow that occurs in thyrotoxicosis, as demonstrated by Wisham and co-workers[4] for leg muscle.

Inasmuch as the acceleration in removal of Na^{24} from the orbit in hyperthyroidism is not abolished or significantly altered by the presence of definite ophthalmopathy of either the severe or the mild form, support is not lent to the concept that venous obstruction has to do with the development of proptosis or of the accompanying edema. Not only is the acceleration of removal rate in hyperthyroidism not abolished, but there is no undue delay in those patients with severe ophthalmopathy who are also euthyroid, and this is also evidence against passive obstruction to venous outflow.

The findings of the present study agree with the conclusion of Whitnall [5] that the venous anastomoses of the orbit are so rich as to make it unlikely anatomically that passive congestion would play a role in the production of exophthalmos. If venous obstruction is not present, the instances in which removal of sodium is actually increased in euthyroid patients with severe ophthalmopathy suggest that the edema and the other eye changes result from the increased capillary permeability

TABLE 4.—*Time (Minutes) Required to Reduce Initial Na^{24} Count to One-Eighth (Arranged According to Duration of Ocular Signs)*

Duration of Ocular Signs	Type of Eye Change		Duration of Ocular Signs	Type of Eye Change	
	Mild	Severe		Mild	Severe
Less than 6 mo.	24	34	More than 6 mo.	21	42+
	24	16		22	32
	20	20		32	50
	..	27		43	39
	..	39		27	..
	..	34		40+	..

and increased arteriolar dilatation and blood flow of an active inflammatory state. In these patients, any effect of hyperthyroidism upon removal rate probably can be excluded.

The presently outlined procedure with Na^{24} does not reveal a significant difference between the responses of the mild and the severe forms of ophthalmopathy associated with Graves' disease. The removal rate of Na^{24} has not been determined for other intraorbital processes which occasionally cause proptosis. It is possible that studies of the procedure might possibly serve to differentiate these from the thyroid eye disorders.

SUMMARY AND CONCLUSIONS

The rate of disappearance of Na^{24} injected in the orbital fat has been measured in patients with the mild and severe forms of eye change of hyperthyroidism and in euthyroid, control subjects.

The data suggest that venous obstruction is not the factor responsible for the edema and proptosis associated with the ophthalmopathies of thyroid disease, particularly the severe form. Instead, an active inflammation with arteriolar dilatation and increased capillary permeability is suggested as the responsible mechanism for the eye disorders of Graves's disease.

Dr. Edith H. Quimby, of the Department of Radiology, gave invaluable assistance throughout the work.

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COMPARISON OF FLICKER PERIMETRY WITH STANDARD PERIMETRIC METHODS

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NINETY selected patients from the University of Michigan ophthalmology clinic have been studied with both flicker fusion and standard perimetric methods. The results obtained will be presented and analyzed to determine the comparative value of the two means of testing. The patients were chosen on the basis of known pathologic changes likely to give field defects. As is obvious from the protocols at the end of the paper, not all fields showed defects; however, the normals are included to illustrate the diversity of disease processes studied. In each patient both types of field testing were performed by the same examiner. Any positive findings by one method were very carefully tested by the other before concluding that either type of field examination was superior. The performance of both tests by the same examiner diminishes the possibility of erroneous conclusions by an enthusiastic flicker perimetrist, who may find lesions overlooked by routine standard perimetry performed either by a technician or by an inexperienced resident. In the present series a most careful effort was made to obtain the utmost information from each type of field without discrimination in favor of one or the other.

The method used was described in detail by Miles,[1] wherein a Strobotac (electronic stroboscope) bulb was mounted on a wand, shielded with thin white paper (to avoid confusion due to irregular illumination within the bulb), and presented 1 meter in front of the patient, on a tangent screen in a lighted room. The rate of flicker was steadily reduced until the patient reported he was first able to detect the intermittent illumination. Flicker fusion is recorded as the smallest number of flashes per second seen as a constant light. Patients have been encountered who cannot perform one type of test, yet do very well with the other. There are persons who constantly follow or are confused by standard test objects, yet do well with flicker. On the other hand, some patients perform well with standard perimetry and claim to see flicker at impossible rates, such as 600 a second.

Certain advantages have been claimed for flicker fields,[2] the chief of which is that the rapid rate of stimulation will demonstrate earlier defects in the visual pathways than can be found by ordinary test objects, including red. Also, flicker

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perception is very little affected by refractive errors, which may obscure ordinary test objects or even produce "false scotomata." [3] Since flicker fusion is a numerical value, quantitative perimetry is rapidly performed without the necessity of changing the size of the test objects. Miles's carefully documented papers imply that in all the cases he has examined * flicker fields have been equal to or superior to routine fields, and in no case inferior. A practical point in favor of the standard method is that it is more familiar and meaningful to the ophthalmologist and the neurologist than is the new and somewhat startling array of numbers.

PRESENT INVESTIGATION

The 90 patients of this series have been grouped according to types of pathologic change. The cases in each group have been further subdivided, as follows:

Fields in Flicker and Standard Perimetry in Various Pathologic Changes

	Same by both methods	Flicker definitely superior	Flicker questionably superior	Standard perimetry definitely superior	Standard perimetry questionably superior
Abnormal fields in neurologic disorders	8	6	2	4	
Glaucoma	6	1	1		
Macular lesions	5			2	
Retinal detachment	2			2	
Hysteria	2			1	2
Cataract	6	1			
Hypertension	7		3		
Normal fields in neurologic disorders	22				
Assorted disorders with normal fields	8				

1. Same information obtained from the two types of perimetry
2. More information obtained from flicker perimetry
3. More information obtained from standard perimetry

The accompanying table gives a brief summary of the findings. The present discussion will follow the grouping of cases indicated above. Pertinent examples will be cited, and a brief summary of each of the other cases, arranged in the order of consideration, is presented at the end of the paper.

A. Abnormal Fields in Neurologic Disorders.—Of 20 cases in this group, definitely superior information was obtained by flicker fields in 6 and by standard fields in 4. Figure 1 (F. G.) illustrates marked depression of flicker values in the right eye, associated with a postconcussion syndrome, right-sided temporal decompression (surgical), paresis of the right trochlear nerve, ataxia with falling to the

* References 1 and 2.

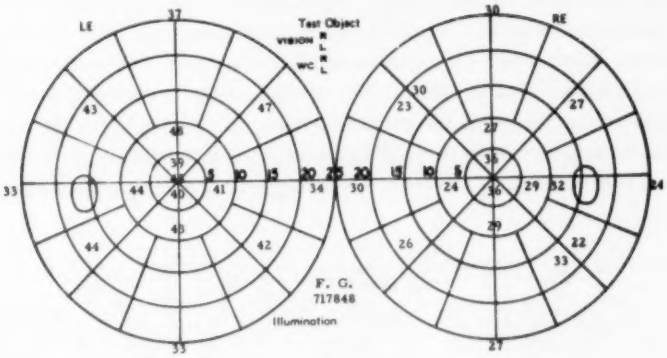

Figure 1

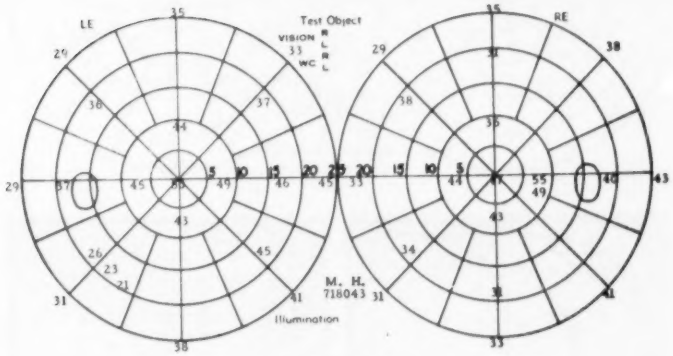

Figure 2

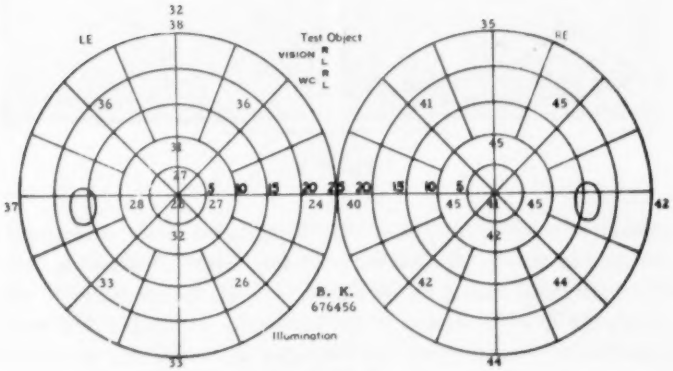

Figure 3

right, and a bilateral Babinski sign. Standard fields in this case were perfectly normal, including those with small red objects. Figure 2 (M. H.) illustrates a left homonymous hemianopsia on a suspected vasospastic basis, associated with slurred speech and ataxia. This defect was reproduced on two tests three days apart and had disappeared, along with the patient's symptoms, a week later. At no time was it evident by standard perimetry. Figure 3 (B. K.) illustrates central depression of flicker in the left eye in a case of recovering retrobulbar neuritis with 6/6 vision

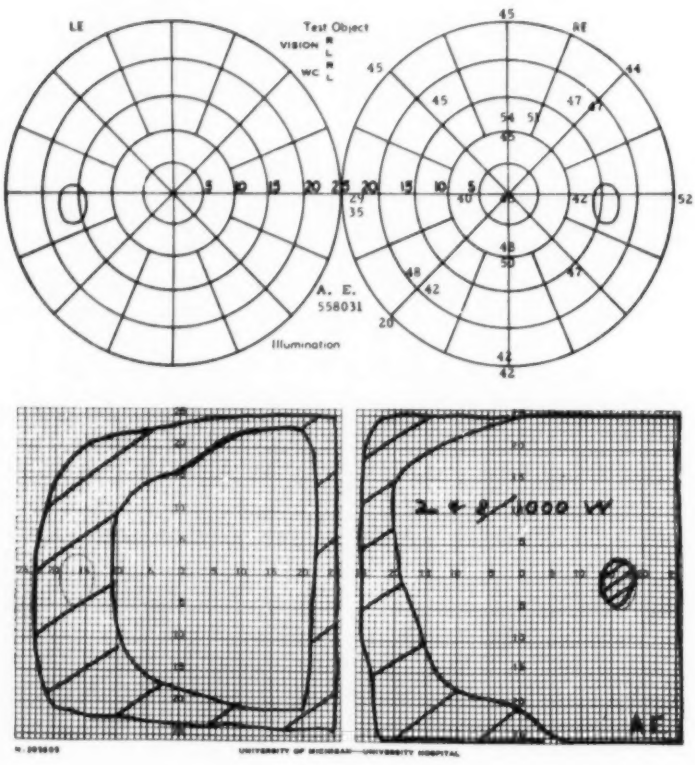

Figure 4

and no central scotoma to 0.5/1000 red. Five flicker fields determined on this patient during one month all demonstrated this central depression. Her flicker fusion values decreased during menstruation. During the treatment of retrobulbar neuritis patients with corticotropin at the University Hospital it has been a fairly common experience to obtain sufficient remission so that central scotomata can no longer be demonstrated by standard fields. In all these cases, however, it has been possible to follow the improvement of the patient by charting the gradually rising central flicker values, which are depressed long after standard field scotomata vanish.

Figure 4 (A. E.), from a patient with a brain tumor, is evidence that not all neurologic field defects are demonstrated more clearly by flicker perimetry. Although a left homonymous hemianopsia is suggested by these flicker fields, the standard fields show the defect much more clearly. Two patients (T. G. and S. H.) showed a loss of temporal crescent and a peripheral constriction beyond 40 degrees. Since flicker testing was confined to the central 30 degrees of the tangent screen, more peripheral defects were not detected.

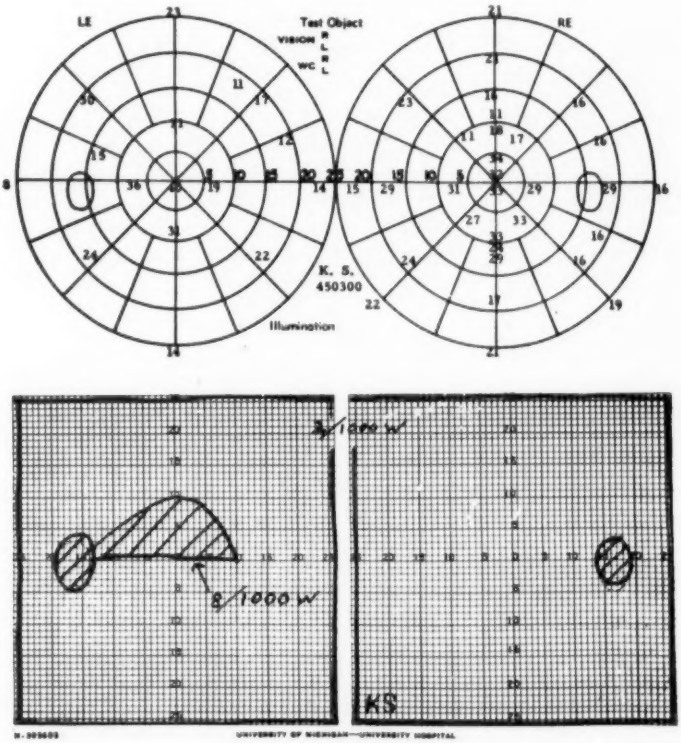

Figure 5

B. Glaucomatous Fields.—Although only eight patients with glaucoma were examined by both flicker and standard perimetry, the examiner was fortunate in finding the patient (K. S.) whose fields appear in Figure 5. This patient had an obvious Bjerrum scotoma elicited by both methods in the left eye and by flicker perimetry only in the right eye. Every attempt was made to elicit a scotoma in this area with small standard test objects, but without success.

C. Macular Lesions.—Patients with fairly large macular lesions showed obvious scotomata by both methods, but this was certainly not true of small lesions. Figure 6

(R. E.) shows by standard testing multiple very small paracentral scotomata in both eyes, on the basis of minimal central chorioretinitis. Vision was 6/4.5 O.U., and flicker testing showed no corresponding areas of decreased flicker fusion frequency. Figure 7 (W. J.) presents a similar case, with myopic central degeneration, vision was correctible to no better than 6/15, and small scotomata were shown in standard fields, but no corresponding drop was shown by flicker perimetry.

D. Retinal Detachment.—Probably also on the basis of very minute macular pathology are the findings in a case of almost complete detachment in the right eye

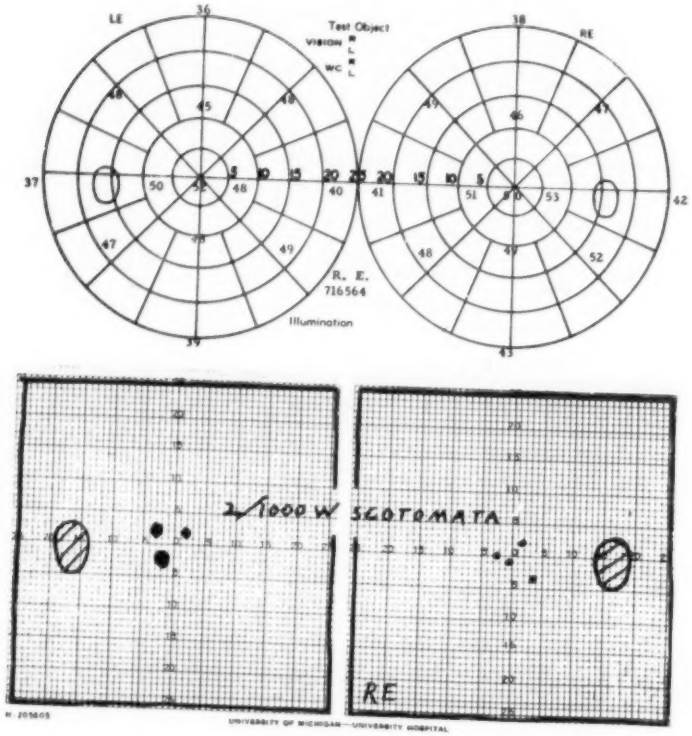

Figure 6

involving the macula, which was successfully operated upon one year previous to the present examination. The vision was 6/30, and standard fields showed a 3-degree central scotoma to 1/1000 white, as illustrated in Figure 8 (R. W.). The accompanying flicker field shows no hint of such pathology, with a recorded flicker frequency of 51, a record for the right eye, slightly higher than the frequency of 49 a second recorded for the normal (left) eye. In another case (J. G.), with detachment beyond 30 degrees in the periphery, the lesion was readily detectable on the perimeter, but not by the flicker test done on the 30-degree tangent screen.

E. Hysteria.—Only five cases of hysteria were studied in this series. There were two cases with classic tubing shown by standard perimetry who presented peripheral depression with flicker perimetry. It depends on one's point of view whether this means that flicker perimetry is superior because it proves peripheral retinal function to be present, or that it is inferior because the field may not show truly tubular characteristics. Figure 9 (L. F.) presents a case which showed definite tubing by standard perimetry and yet an essentially normal flicker field.

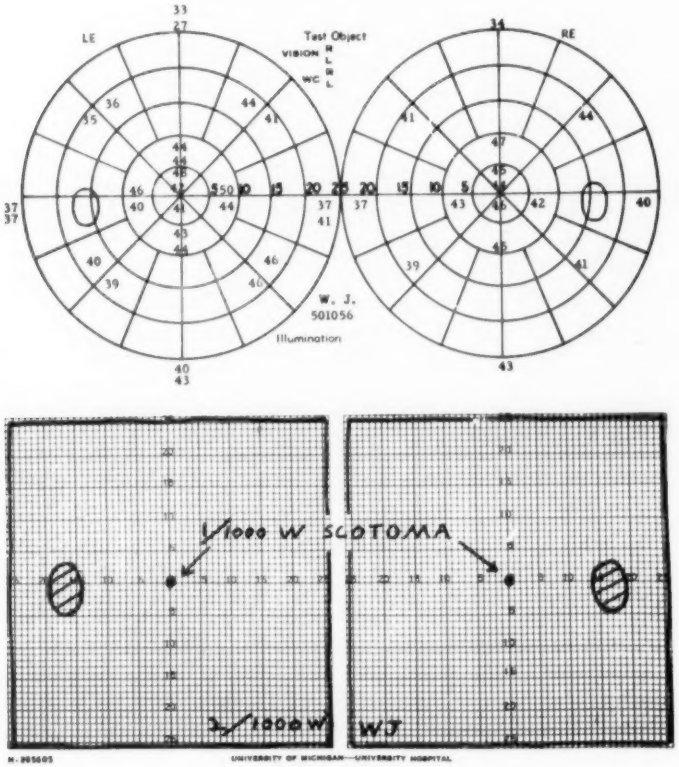

Figure 7

This patient would state that, although he "could not see anything" in the periphery, he could consistently "sense a flickering" at the values shown for the periphery!

F. Cataract.—Both methods of examination showed generalized depression of the field proportionate to the density of the lens opacity. It was possible to demonstrate the presence of retinal detachments behind cataracts by both methods. No prognostic correlation was obtainable between flicker values and postoperative vision, since with a dense cataract flicker values could be as low as 14 a second and the patient still obtain good postoperative vision. Flicker values were almost the

same in aphakic patients with or without their strong correction, clearly proving the virtual independence of flicker values from refractive errors. One patient with a dense cataract in a glaucomatous eye, faulty light projection, and no color perception was spared a needless operation because of complete absence of flicker perception. He was unable to recognize flicker with the bulb head at only 1 in. (2.5 cm.) from the eye.

G. Hypertension, Aging, and Other Factors.—Figure 10 (C. R.) illustrates the general depression of flicker values obtained in a 54-year-old man with Grade

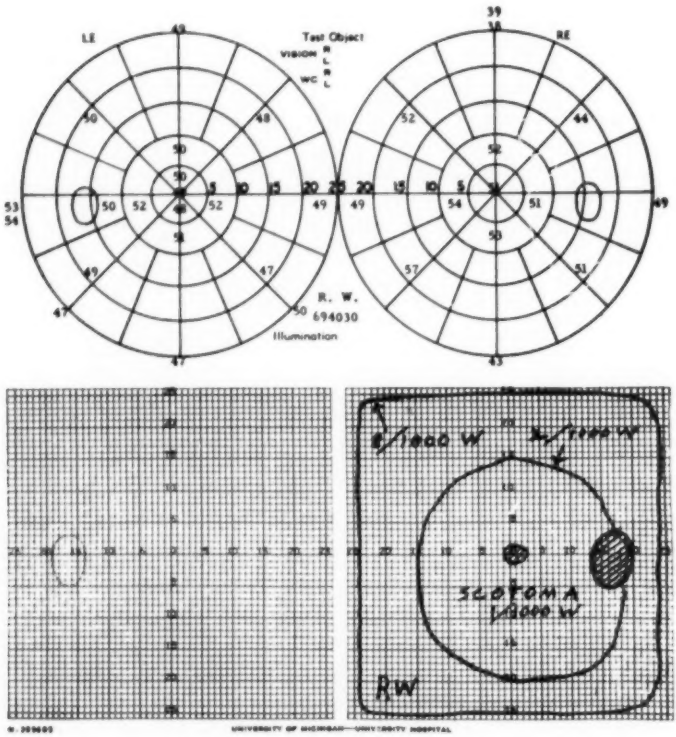

Figure 8

III hypertensive retinopathy (Keith-Wagener classification). Standard fields were normal. Such depression may be found in a great number of conditions, which appear to act by decreasing the nutrition of the neural elements and may confuse the interpretation of flicker fields.

H. Normal Fields in Assorted Cases.—A wide variety of cases (see protocols at end of paper) were studied with the hope of finding pathologic fields by one or the other method and further establishing indications for the use of flicker or standard perimetry. They are included to show the variety of clinical material available for this study.

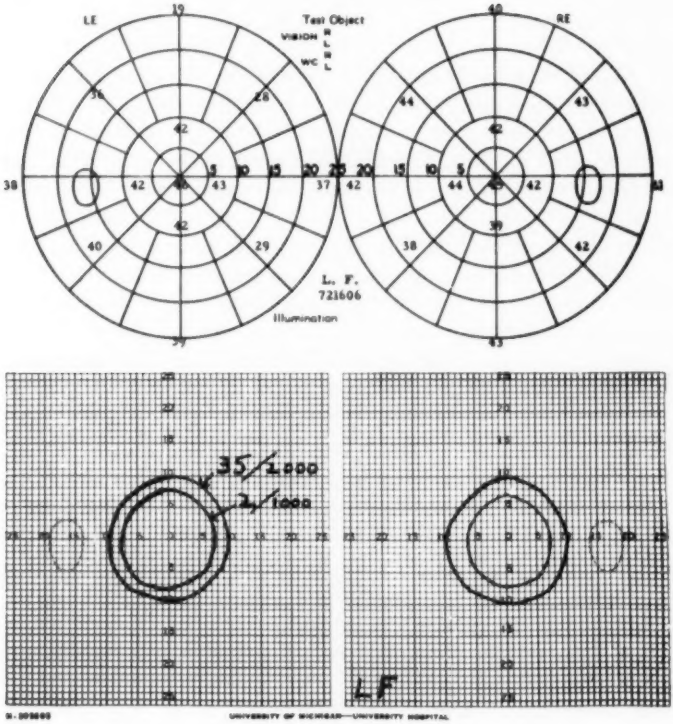

Figure 9

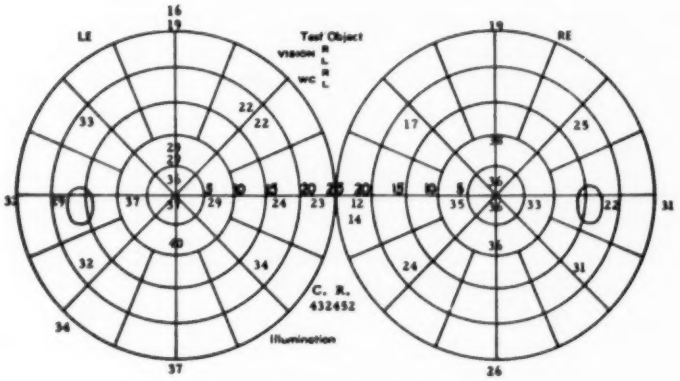

Figure 10

COMMENT

Since the flicker bulb is several centimeters in diameter (2 by 3 arc degrees at 1 meter), one might reasonably expect that a tiny scotoma caused by a very small localized chorioretinal lesion could not be charted by the flicker method. Figures 6, 7, and 8 demonstrate such findings. If a small scotoma were caused by a minute lesion in the occipital lobe or the optic radiation, it might still not be detectable by flicker because the adjacent visual units are perfectly normal and can detect the flickering bulb, which is larger than the scotoma. This holds true only for small scotomata—large areas of chorioretinitis or hemianopsias are readily demonstrable by flicker.

On the other hand, the small scotoma of retrobulbar neuritis can be detected readily by flicker perimetry. This finding implies that retrobulbar neuritis is a fairly widespread nutritional disorder, affecting enough of the papillomacular bundle and adjacent fibers to involve a central area larger than the size of the flicker bulb. Whereas one may find a 2-degree central scotoma to 1/1000 white, the same patient will show a more widespread depression to flicker, not limited to such a small area. Flicker perimetry is far more sensitive than standard perimetry in detecting early lesions of the nerve pathways (Figs. 1, 2, 3, and 5).

Depressed flicker fusion frequency values may be obtained often in hypertension; severe illnesses, such as pneumonia, toxemia, or meningitis; glaucoma; cataract, and psychiatric disorders, and occasionally in an apparently normal older person. Since such fields are consistently and reproducibly depressed, there is obviously some cause present. However, for purposes of diagnosis, such a flicker field is rather confusing, and the frequency of generally depressed flicker fusion is so great that it cannot be given the diagnostic significance of a constricted or depressed standard field. In this respect flicker fields may be said to be too sensitive, inasmuch as they apparently detect minor nutritional defects.

If flicker testing is performed with the tangent screen, it shares the same limitations of ordinary screen testing, namely, inability to detect lesions beyond 30 degrees from fixation. Such field defects include temporal crescent lesions, peripheral chorioretinitis, tumor or detachment, peripheral constriction, and mid-peripheral annular scotomata. All these conditions are susceptible to detection by flicker studies carried out in the periphery.

SUMMARY AND CONCLUSIONS

Ninety selected patients were studied by both flicker and standard perimetry, and the following conclusions were drawn:

1. Flicker perimetry is demonstrably superior to standard perimetry in detecting early lesions of the visual pathways, provided such a lesion is extensive enough to include the whole area of the flicker bulb in the scotoma. Such lesions include retrobulbar neuritis, which depresses the function of a large group of central retinal fibers, yet produces only a small scotoma by standard methods.

2. Standard perimetry is demonstrably superior to flicker perimetry (which utilized a large target bulb) in detecting very small scotomata, provided such a lesion is produced by sharply defined pathology, e. g., a small area of chorioretinitis or a small occipital lobe lesion.

3. General depression of the flicker field can be produced by a wide variety of general diseases and degenerations, and, therefore, such fields are of considerably less significance than a constricted or depressed field obtained by standard perimetry.

4. Any method of perimetry, including flicker fusion testing, which examines only the area within 30 degrees of the fixation point cannot detect lesions of the more peripheral nerve fibers only.

SUMMARY OF CASES STUDIED

A. Abnormal Fields in Neurological Disorders

1. Same Information As Regular Fields

(*a*) J. E., 25-year-old white woman with postpartum meningitis and concentric constriction

(*b*) J. B., 45-year-old white man with syphilitic optic atrophy and loss of two-thirds of area of field

(*c*) C. L., 28-year-old white man with mental retardation and disc pallor; concentric constriction

(*d*) H. O., 60-year-old white woman with cerebrovascular accident and right inferior quadrantanopia

(*e*) B. S., 55-year-old white man with pituitary tumor and incongruous left inferior quadrantanopia

(*f*) S. H., 33-year-old white man with nystagmus and left facial pain, with concentric constriction

(*g*) E. F., 41-year-old white woman with probable multiple sclerosis and concentric constriction

(*h*) T. S., 24-year-old white man with retrobulbar neuritis and large central scotoma

2. Less Information Than Regular Fields

(*a*) A. E., 63-year-old white woman with suspected brain tumor and incomplete left homonymous hemianopsia; latter detected on flicker field but much less evident

(*b*) L. B., 37-year-old Negro man with suspected brain tumor and inferior left homonymous paracentral scotoma, not well shown on flicker field

(*c*) T. G., 28-year-old white woman with posteclamptic headaches and loss of temporal crescent in left eye, not detected by flicker testing in central 30-degree area

(*d*) S. H., 31-year-old white woman with postconcussion syndrome and loss of peripheral field beyond 40 degrees, defect not very evident with flicker testing in central 30-degree area

3. More Information Than Regular Fields

(*a*) F. G., 18-year-old white youth with postconcussion syndrome and right temporal decompression; paresis of right fourth nerve, bilateral Babinski sign, ataxia with falling to right; marked depression of flicker values for O.D., but perfectly normal standard field, including that for red test objects

(*b*) M. H., 43-year-old white woman, with probable cerebrovascular accident, slurred speech, ataxia; left homonymous hemianopsia in two flicker fields three days apart; normal flicker field one week later, at which time symptoms had markedly improved; never any defect in standard fields

(*c*) A. K., 58-year-old Negro with syphilitic optic atrophy and vision 6/30 and J 1 with strong add; marked central depression; central scotoma not demonstrable with tangent screen or stereocampimeter, due to poor fixation

(*d*) P. P., 35-year-old white man with multiple sclerosis; marked central depression with flicker, no scotoma with standard perimetry

(*e*) B. E., 31-year-old white woman with recovering retrobulbar neuritis; marked central flicker depression in five fields during a month's time, with 6/6 and J 0 and no central scotoma to 0.5/1000 red

(*f*) K. D., 25-year-old white woman with recovering retrobulbar neuritis; marked central flicker depression on two occasions, and only questionable scotoma to 0.5/2000 white

(*g*) E. G., 28-year-old Negro woman with repeated epileptic seizures and general depression of flicker values; normal standard fields

(*h*) V. R., 61-year-old white woman with suspected brain tumor and hypertension; peripheral depression of flicker fields and normal standard fields

(*i*) J. E., 22-year-old white man with retrobulbar neuritis and superior central scotoma in O.D. clearly demonstrable with flicker, but confused by unreliable responses on tangent screen

B. Glaumatous Fields

1. Same Information As Regular Fields

(*a*) C. C., 54-year-old white woman with controlled chronic simple glaucoma; normal fields

(*b*) P. G., 41-year-old white woman with controlled chronic simple glaucoma; normal fields

(*c*) M. S., 48-year-old white woman with enucleation O.S. for glaucoma and iridencleisis O.D. for pressures which had reached 64 mm.; normal field O.D.

(*d*) M. D., 63-year-old white woman with enucleation of O.D. for glaucoma; O.S. controlled with pilocarpine; right upper field loss and central depression by both methods

(*e*) N. P., 53-year-old white man with vision equal to counting fingers O.D. and 6/9 O.S.; marked constriction of both types of field

2. Less Information Than Regular Fields

No patients

3. More Information Than Regular Fields

(*a*) K. S., 52-year-old Negro woman with classic Bjerrum scotoma O.U. by flicker perimetry, but only in O.S. by tangent screen examination; chronic simple glaucoma, on pilocarpine therapy; O.D. normal to 1/1000 white without Bjerrum or Seidel scotoma, normal to small red objects

(*b*) R. R., 60-year-old white man with loss of O.D. from chronic glaucoma; general depression of flicker values in O.S., normal by standard perimetry

C. Macular Lesions

1. Same Information As Regular Fields

(*a*) C. F., 15-year-old white girl with central chorioretinitis O.U. and large scotoma (5 degrees O.S. and 20 degrees O.D.)

(*b*) L. S., 22-year-old white man with central chorioretinitis O.S. and 30-degree scotoma

(*c*) D. C., 43-year-old white man with central angiospastic retinopathy O.D., with 2-degree scotoma to 1/1000 red and flicker 42 to 44 a second, as compared with 47 a second for O.S.

(*d*) H. H., 50-year-old white man with central verrucous changes of macula in O.U., but vision still 6/4.5 and J 0; normal fields

(*e*) R. B., 65-year-old white man with myopic degeneration in O.U. and vision equal to counting fingers; concentric constriction and small central scotoma O.U.

2. Less Information Than Regular Fields
   (*a*) R. E., 26-year-old white man with minimal paracentral corioretinitis O.U.; 1- to 2-degree paracentral scotomas O.U. with 1/1000 white, although flicker values centrally were 50 and 52 per second and areas of depression could not be found; vision 20/15 O.U.
   (*b*) W. J., 23-year-old white man with myopic degeneration (—16.00 D., O.U.); vision 6/15 and 6/30; central flicker not depressed (44 to 48 a second), but definite 1-degree central scotomata O.U. with 1/1000 white
3. More Information Than Regular Fields
   No patients

D. Retinal Detachment
1. Same Information As Regular Fields
   (*a*) H. O., 42-year-old white man with inferior detachment and dense cataract; superior defect by both methods
   (*b*) H. B., 49-year-old Negro man with inferior retinal separation, treated by diathermy; superior defect by both methods
2. Less Information Than Regular Fields
   (*a*) R. W., 17-year-old white youth with almost complete retinal detachment operated on successfully one year before; vision 6/30, with 3-degree central scotoma to 1/1000 white and considerable contsriction to 2/1000 white; perfectly normal flicker values (over 50 a second) throughout central 30-degrees of field, including fixation point
   (*b*) J. G., 25-year-old white man with inferior retinal detachment secondary to von Hippel's disease; superior defect beyond 30 degrees, just barely detected by central flicker field
3. More Information Than Regular Fields
   No patients

E. Hysteria
1. Same Information As Regular Fields
   (*a*) R. S., 51-year-old white woman with 10-degree tubular field by both methods
   (*b*) B. N., 13-year-old white girl with 10-degree tubular field by both methods
2. Less Information Than Regular Fields
   (*a*) J. O., 30-year-old white woman with definite tubing by regular fields; only peripheral depression with flicker
   (*b*) C. S., 21-year-old white man with definite tubing by regular field; only general depression with flicker
   (*c*) L. F., 27-year-old white man with 7-degree tubular field to all sizes of test objects, but perfectly normal flicker field!
3. More Information Than Regular Fields
   No patients

F. Cataract
1. Same Information As Regular Fields
   (*a*) H. O., 42-year-old white man with dense cataract, inferior detachment, and superior field defect
   (*b*) H. B., 49-year-old Negro man with advanced cortical cataract, old surgically treated inferior detachment, and superior field defect
   (*c*) L. R., 15-year-old white male with dense traumatic cataract, foreign body localized in inferior globe, and superior field defect
   (*d*) M. M., 75-year-old white woman with dense cataract; vision for hand movement only and flicker at 14 a second; good postoperative results

(*e*) I. R., 82-year-old white woman with central scotoma; flicker values 2 to 7 a second higher with +9.00 D. correction than without

(*f*) N. V., 62-year-old white woman with 6/30 vision, cataract O.U. and general field depression

2. Less Information Than Regular Fields
No patients

3. More Information Than Regular Fields

(*a*) M. S., 70-year-old white woman with cataract in old glaucomatous eye; poor light perception but absolutely no flicker perception at any rate, even only 1 in. from eye; flicker seen with good eye

G. Hypertension, Aging, and Other Factors

1. Same Information As Regular Fields

(*a*) A. P., 36-year-old white man with Grade III hypertensive retinopathy and normal field

(*b*) N. T., 37-year-old Negro woman with Grade IV hypertensive retinopathy and slightly constricted fields

(*c*) W. M., 45-year-old Negro with Grade II hypertensive retinopathy and normal fields

(*d*) R. F., 31-year-old white woman; three years of posteclampsia with blood pressure 205/130 and papilledema; enlarged blind spots

(*e*) W. M., 60-year-old white man with severe arteriosclerosis and systolic pressure to 195 mm. Hg; slight general depression with flicker and normal regular field

(*f*) A. D., 55-year-old white man; blood pressure 210/110 with normal fields and Grade II hypertensive retinopathy

(*g*) W. G., 39-year-old white man with blood pressure to 170 systolic; normal fundus and fields

2. Less Information Than Regular Fields
No patients

3. More Information Than Regular Fields

(*a*) C. R., 54-year-old white man with Grade III hypertensive retinopathy, considerable depression of flicker field, and normal regular field

(*b*) S. K., 54-year-old white man with Grade IV hypertensive retinopathy, marked depression of flicker field, and normal regular field

(*c*) L. M., 33-year-old white woman with malignant hypertension, postsplanchnicectomy, hypertensive encephalopathy, marked depression flicker field, and normal regular field

H. Normal Fields in Assorted Cases (by both methods)

(*a*) L. D., 35-year-old Negro woman with posterior inferior cerebellar artery syndrome

(*b*) C. D., 29-year-old white man with postconcussion syndrome and grand mal seizures

(*c*) S. L., 45-year-old white woman with nine years of incapacitating left-sided migraine

(*d*) C. C., 56-year-old white man with 10 years' acromegaly and x-ray treatment of pituitary

(*e*) E. G., 64-year-old white woman with two months of auditory agnosia and jargon aphasia

(*f*) C. T., 22-year-old white man with two years of severe grand mal seizures

(*g*) C. C., 29-year-old white man with petit and grand mal seizures since infancy

(*h*) F. C., 32-year-old white man with two years of right frontal headache, numbness of left side of face and left arm, and psychomotor seizures

(*i*) E. F., 44-year-old white man with internal carotid thrombosis, central right seventh nerve paralysis, aphasia, and right hemiparesis

(*j*) B. D., 45-year-old white man with six months' progressive paresthesia of right arm (brachial plexus lesion?)

(*k*) W. L., 37-year-old white man with multiple sclerosis

(*l*) L. K., 59-year-old white woman with depressive psychosis and questionable degeneration of right temporal lobe

(*m*) J. A., 58-year-old white man with progressive right hemiparesis due to cerebral metastasis

(*n*) W. R., 41-year-old white man with delirium tremens, personality disorder, and convulsions

(*o*) D. B., 18-year-old white girl with grand mal and aura of left facial paralysis

(*p*) F. P., 58-year-old white man with cerebrovascular accident, right hemiparesis, and paretic left medial rectus

(*q*) A. B., 49-year-old white man with organic brain syndrome and amnesia

(*r*) D. K., 17-year-old white girl with Sydenham's chorea, mental retardation, epileptic equivalents, and behavior disorder

(*s*) C. C., 23-year-old white man with three years of psychomotor seizures

(*t*) A. W., 62-year-old white man with probable cerebrovascular accident, causing left facial numbness, left corneal anesthesia, deafness of left ear, and staggering to left

(*u*) P. B., 55-year-old white man with 15 years of tinnitus, marked anisocoria, and poor attention span

(*v*) A. F., 17-year-old white youth with grand mal seizures for two months

(*w*) D. F., 26-year-old white man with 18 months of severe headache, unknown etiology

(*x*) R. N., 56-year-old white man with +5.00 D. hyperopia, moderate retinal arteriosclerosis, and glial veil overlying disc

(*y*) T. B., 49-year-old white man with 23 mm. of thyrotropic exophthalmos

(*z*) E. G., 34-year-old white woman with six-week visual loss six years before; vision normal now

(*a'*) G. B., 28-year-old white woman with miotic and fixed left pupil since head trauma 20 years before

(*b'*) M. D., 31-year-old white woman with headaches and frequent fainting

(*c'*) L. L., 35-year-old white woman with severe headaches

(*d'*) N. H., 20-year-old white woman with anisometropia and drusen of optic nerve

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BAND KERATOPATHY IN VITAMIN D INTOXICATION

Report of a Case

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THE ASSOCIATION of abnormal serum calcium with ocular manifestations was first reported by Meesmann in 1938. His case was one in which band-shaped opacities of the cornea and opacities of the conjunctiva developed when overdosage in treatment of hypoparathyroidism following thyroidectomy caused a high serum calcium. Since then, 36 cases of disturbed calcium metabolism with calcium deposits in the cornea, or in the conjunctiva, or in both have been reported.*

Such deposits appear as subconjunctival crystals or white flakes, and as diffuse, superficial, gray corneal opacities in the palpebral fissure, denser near the limbus and fading toward the center of the cornea. Usually there is a clear area of 1 or 2 mm. between the opacities and the limbus, but two of the cases reported by Ojers and Alfano [3] and the present case did not have this feature. Welsh and Howard [4] reported that chemical analysis of affected conjunctiva on biopsy showed what was probably a calcium salt.

The 36 cases previously reported were associated variously with hyperparathyroidism, overtreatment for hypoparathyroidism, sarcoidosis, renal disease, and vitamin D intoxication. Many of the patients had nephrocalcinosis or nephrolithiasis. The case to be reported was one of vitamin D intoxication with band keratopathy and nephrocalcinosis.

REPORT OF CASE

J. D., a 61-year-old white man, was admitted for study to the Benjamin Franklin Clinic of the Pennsylvania Hospital in August, 1952, complaining of anorexia and constipation of two months' duration, weakness for six months, and a 30 lb. (13.6 kg.) weight loss during the previous year. In the treatment of rheumatoid arthritis, 150,000 U. S. P. units of vitamin D had been taken daily in the form of Darthronol (a multivitamin preparation) capsules for two years prior to admission. This represented a total consumption of 109,500,000 U. S. P. units of vitamin D.

Laboratory tests showed a normal urine, with a phenolsulfonphthalein excretion of 10% in 15 minutes and a total excretion of only 36% in two hours. The blood studies showed a hemoglobin content of 10.4 gm. per 100 cc., 3,200,000 red blood cells, and 6,800 white cells. The uric acid was 5.4 mg., total protein 6.2 gm., albumin 4.3 gm., phosphorus 4.6 mg., and serum calcium 14.6 mg., per 100 cc.

Limbal opacities were easily seen in the area of the palpebral fissure on both corneas temporally and nasally, being more pronounced in the right eye and more conspicuous on the temporal side in both eyes. Slit-lamp examination showed these opacities to lie just beneath the epithelium. They were gray and irregular in shape, extending to the limbus at several points and confined to the area of the palpebral fissure. Toward the central portion of the cornea these lesions advanced 2 or 3 mm., fading away gradually. Over the temporal area of the right cornea, where

* References 1 through 4.

the opacification was densest, was roughening of the epithelium. No deposits were seen in the conjunctiva. The eyes were otherwise normal, and vision was correctible to 6/6 in both eyes.

A diagnosis of vitamin D intoxication was made. The intake of vitamin D was stopped, and a low calcium diet was prescribed. Blood serum calcium fell to 10.8 mg. per 100 cc. in September, 1952, and to 10 mg. per 100 cc. in October, with considerable relief of subjective symptoms. When the eyes were reexamined in December, 1952, the corneal opacities could be clearly seen only with the slit lamp and the corneal epithelium was quite smooth. In March, 1953, the corneas were entirely clear and smooth; the phenolsulfonphthalein excretion had increased to 45% in 20 minutes, and the serum calcium was 10.9 mg. per 100 cc. It was less pleasing to the patient that the arthritic pains had returned.

COMMENT

Cogan believes that extravascular fluid diffuses into the cornea from the periphery and there, by loss of water through the epithelium, calcium salts are concentrated and precipitated. Thus, the calcium deposits are a direct result of the hypercalcemia.[2]

On the other hand, in a case of renal rickets reported by Ojers and Alfano, no hypercalcemia was found, or any evidence of tissue calcium deposition except

Limbal opacities in a case of vitamin D intoxication.

in the cornea and conjunctiva. Accordingly, these authors have suggested that abnormal mobilization and transportation of calcium, rather than the hypercalcemia itself, causes the calcium deposits.[3]

SUMMARY

This case demonstrates that, whatever the mechanism, band keratopathy and, presumably, nephrocalcinosis may accompany hypercalcemia following excessive vitamin D ingestion. Both these conditions are reversible. The corneal changes do not interfere with vision, but they do serve as a warning of renal damage, which might prove fatal.

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VASCULAR LESIONS IN DIABETES MELLITUS

III. Pathogenesis

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ATHEROSCLEROSIS, medical sclerosis, and arteriolar sclerosis all occur more frequently in diabetic than in nondiabetic patients. The clinical features of these conditions in diabetics were reviewed in previous reports.* As a cause of morbidity and mortality, atherosclerosis is the most important form of arteriosclerosis by far.

As has been pointed out elsewhere,[4] it is agreed at present that the specific lesions of diabetes are in the capillaries and venules of the retina and glomerulus, i.e., retinopathy and intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease). Diabetic retinopathy passes through successive stages, beginning with the microaneurysm and lesions of the venules. The exudates are small, pinpoint lesions in the early stages, coalesce to form larger, waxy exudates, but do not take on the star-shaped configuration one sees, for example, in albuminuric retinopathy. In the final stage there is hemorrhage into the vitreous and/or the fully developed picture of retinitis proliferans.

Very recently, Ashton † has shown that retinal microaneurysms are not seen solely in diabetes but are encountered also in a wide variety of clinical disorders in nondiabetics, and even in some supposedly normal eyes; but in such cases the aneurysms do not progress to any significant degree of retinopathy. For example, lesions such as these have been reported following obstruction of the central retinal veins, and great numbers of retinal capillary aneurysms have been reproduced in this manner in cats.[7] Givner [8] has frequently observed exudates similar to those of diabetic retinopathy which were due to inflammatory edema. Unlike diabetic retinopathy, however, such exudates are absorbed gradually, leaving no traces. A few microaneurysms may occur in nondiabetic cases of malignant hypertension.

Many questions remain unanswered. Why do the specific vascular lesions of diabetes have a predilection for these particular sites? By what mechanism or mechanisms are these changes initiated? Some aspects of the pathogenesis of the retinal and glomerular lesions will be discussed herein.

A. ANATOMY AND PHYSIOLOGY OF RETINAL AND GLOMERULAR CIRCULATION

At one time the capillary lesions in diabetic retinopathy were thought to be endothelized petechiae, but all available evidence now points to the initial lesions as being capillary aneurysms. By means of a new stain, which clearly outlines the basement membrane, it was proved that these lesions are true capillary aneurysmal

* References 1, 2, and 3.
† References 5 and 6.

dilatations with both afferent and efferent connections. A more complete discussion of the various factors which might explain the peculiar selectivity of diabetes for the capillaries of the eye and kidney will be published separately by my colleague Dr. David Volk.‡

There is no doubt that hemorrhages occur either by rupture of aneurysms or by diapedesis through the capillary walls. The paramount question is: What factor in diabetes causes the aneurysms and small hemorrhages?

The capillaries of a normal glomerulus are suspended or arranged on a delicate extravascular connective tissue framework, or axial stroma, which is thus an intercapillary substance, termed the mesangium.§ Distinct epithelial and endothelial basement membranes are present in the glomerular tuft. An interstitial space has been described between these basement membranes which is continuous with the interstitial space of the connective tissue stalk of the glomerular lobules.[9] In the interstitial space of the stalk there are normally a substantial number of "interstitial" cells, which increase with age and with injury. With progressive repair of any glomerular injury, inflammatory cells disappear, and the proliferated interstitial cells progressively lay down connective tissue fibrils, mainly in the interstitial space of the stalk. The obliteration of the capillaries depends to a great degree on the amount of connective tissue laid down about the circumference of the capillaries, i. e., between the capillary and the epithelial basement membranes.[9] The end-result of these processes is the hyalinized scar.

In the glomerulus of diabetic patients the capillary is patent, at times engorged, and may even be aneurysmal. The lesion of intercapillary glomerulosclerosis observed is a particular form of thickening of the axial stroma. In far-advanced lesions the nodular masses increase in size; capsular adhesions with periglomerular fibrosis may develop, and, eventually, the capsular space is completely obliterated and the glomerular tuft totally fibrosed. In the majority of sections narrowing of the afferent arterioles is continuous with the axial fibrosis of the glomeruli. The occasional case with minimal intercapillary glomerulosclerosis, unassociated with afferent arteriolar lesions, strongly suggests that intercapillary glomerulosclerosis is not simply an extension of the nonspecific arteriolar lesion, but is, rather, a specific glomerular degenerative change occurring in diabetes.[14]

The exact site of origin of the nodular material in glomerulosclerosis, its chemical composition, and its specific staining reactions are all problems of intense interest at the present time. Allen,[15] among others, has pointed out certain qualities of this hyalin material which help to differentiate it from hyalin in other nephropathies, for example, its relative resistance to tryptic digestion and its curious lamination and fibrillar structure. McManus[13] offers the intriguing suggestion that the hyalin in the glomerular and retinal lesions might originate from some abnormal mucoprotein in plasma.

The formation of the exudates appears to be explained more readily by the fact that deposits of hyalin and lipid material tend to occur in any inadequately nourished or anoxic tissue. It follows that those areas of the retina where exudates are formed must be ischemic. In the retina the hyalin appears to be deposited (accord-

‡ Volk, D.: Personal communication to the author.

§ References 10 through 12.

ing to Friedenwald ‖) inside the basement membrane of the aneurysm, leading in this manner to an occlusion of the saccular lumen. Ashton ¶ and Friedenwald,# in their histochemical studies, found no distinctive staining characteristics to differentiate the hyalin of the Kimmelstiel nodule from that of the thickened walls of retinal capillary aneurysms.

Although the evidence that the retinal aneurysms and the Kimmelstiel glomerular nodules are concomitant manifestations of the same process appears unequivocal, it does not necessarily follow that the pathogenesis of these two lesions is identical in every respect. Actually, while the retinal capillary and the glomerular capillary are alike in having a well-developed basement membrane, they are different both morphologically and physiologically.

B. PATHOGENESIS OF RETINOPATHY AND INTERCAPILLARY GLOMERULOSCLEROSIS (KIMMELSTIEL-WILSON SYNDROME)

While there is no doubt that retinopathy and intercapillary glomerulosclerosis occur almost exclusively in diabetes mellitus, this fact does not tell us by what mechanism the microaneurysms, small round hemorrhages, exudates, massive hemorrhages, new vessel formation, etc., occur. Needless to mention, ultimately successful therapy hinges upon finding the cause of these lesions. Among the possible x factors which have been proposed is hyperglycemia, in the sense that no sign of diabetes would occur without hyperglycemia (Graefe). Certainly, hyperglycemia and ketonemia, which are present intermittently in some patients, must at least be taken into consideration. Some believe the factor is a long-standing subclinical vitamin deficiency or hypoproteinemia [18]; others, hypercholesterolemia, and still others point to liver dysfunction as the crucial factor. Or may there not be a common factor which produces the diabetes and the vascular lesions simultaneously? Actually, the sum total of our knowledge of the causal factors of retinopathy and intercapillary glomerulosclerosis is still slight.

The pathologic manifestations of retinopathy and the Kimmelstiel-Wilson syndrome may be explained by one of several physiologic processes. There may be changes in the pericapillary supporting tissue of such a degree that the normal intracapillary pressure will then cause rupture of the endothelium. One possibility which comes to mind is increased hyaluronidase activity and liquefaction of the pericapillary supporting tissues, which contain hyaluronic acid. Another possibility is endothelial damage through inhibition of production of the intraendothelial cement substance, which protects the capillary lining.

Although a satisfactory explanation of the progression and retrogression of retinopathy and glomerulosclerosis is still lacking, a number of points should be kept in mind with respect to these conditions. Progression is reported as frequently in mild as in severe cases of diabetes; it is noted in patients for whom insulin is used as well as in diabetics whose disease is controlled without insulin, and early in the course of the disease as well as late, although more frequently late. The retinal and glomerular lesions are frequently observed in diabetes of more than 10 years' duration; yet many patients with long-standing diabetes never develop

‖ References 16 and 17.
¶ References 5 and 6.
# References 16 and 17.

these lesions. Conversely, the lesions may be static in poorly regulated cases. Sometimes these lesions are discovered before the presence of diabetes is detected and irrespective of whether the diet has been unlimited or restricted. They occur in young as well as in middle-aged and old persons. Small wonder that some authors are inclined to doubt the efficacy of the control of the diabetes in management of these lesions,[19] while other * steadfastly maintain that good control of the diabetes is the only hope of warding off retinopathy and nephropathy. Pending further evidence to the contrary, it is probably wiser to adhere to the latter view.

Tolstoi * postulates that the vascular lesions in the retina and glomeruli are part of a similar process disseminated throughout the entire arteriolar system. Still, it is remarkable that analogous lesions have not been found in other organs, despite careful search by many investigators. Undeniably, retinopathy and glomerulosclerosis coexist with arteriosclerosis or hypertension in some diabetic persons. Increased capillary fragility is associated with retinopathy in many cases, but in many others it is not. Priscilla White [20] suggests that a toxin similar to menotoxin might act as a vascular poison in diabetes.

Recently the vascular lesions seen in man have been produced experimentally. For example, Lukens and Dohan [21] reported intercapillary glomerulosclerosis in a dog in which the diabetes had been largely uncontrolled over a five-year period. Very recently, in Rich's laboratory,† retinal aneurysms were produced in alloxanized rabbits by the administration of cortisone and corticotropin.

1. *Arteriosclerosis and Hypertension.*—Before the advent of insulin, and for many years thereafter, the primary cause of diabetic retinopathy was believed to lie in the accompanying pathologic changes in the arterial tree, and the metabolic disturbances of the disease were accorded at most a secondary role. Such a leading authority as Wagener [23] maintained that diabetic retinopathy did not occur without hypertension and/or arteriosclerosis.‡ Subsequent observations [26] showed that retinal lesions frequently antedated hypertension or arteriosclerosis, forcing a revision of the older views. This changing concept was voiced forcefully by Wagener [27] himself:

> In 1921, I expressed the opinion that, essentially, retinopathy of diabetes is retinopathy of arteriosclerosis. This, I think now, is not true. I doubt now that arteriosclerosis in the retina per se ever produced retinopathy. Certainly it does not produce retinopathy of the type seen in diabetes.

Wagener later observed cases in which retinopathy developed in the absence of any clinical evidence of vascular disease elsewhere in the body.

Some authors, notably Dolger,[19] have postulated a common origin of arteriosclerosis, hypertension, and diabetes mellitus. The coexistence of arteriosclerosis and retinopathy does not necessarily prove a causal relation between these two conditions, since both diabetes and arteriosclerosis are common in the middle and advanced ages. Moreover, arteriosclerosis and essential hypertension occur only infrequently in young diabetic patients.

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* Tolstoi, E., in discussion on Root, H. F.: Complications and Sequelae of Diabetes. Relation to Control, Panel Discussion, 12th Annual Meeting of American Diabetes Association, June 8, 1952.

† Reference 22. Rich, A. R.: John Hopkins Hospital Clinical-Pathological Conference, February, 1952.

‡ References 24 and 25.

That the classical picture of diabetic retinopathy can occur without any discernible evidence of arteriosclerosis is best attested by young diabetic patients in whom neither arteriosclerosis nor hypertension is demonstrable. For example, Givner [8] reported three patients aged 12, 15, and 15 years who had diabetes for 9, 11, and 9 years, respectively, each of whom showed pinpoint lesions and venous dilatation, without arterial changes. Croom was unable to detect arteriosclerotic changes in the retinal vessels of half of 60 patients with long-standing diabetes (up to 26 years). My colleagues and I also fail to find any correlation between retinopathy and atherosclerosis, either in the retinal vessels themselves or elsewhere in the body.[1] Nevertheless, at times the ophthalmoscopic picture is complicated by retinal changes, for example, aging, arteriospasm, or venous obstruction, which have no causal relation to diabetic retinopathy.

Conversely, capillary microaneurysms and the other lesions of diabetic retinopathy are not ordinarily seen in the nondiabetic with atherosclerosis or hypertension. Although the classical retinal and renal changes of diabetes may be complicated by atherosclerosis and hypertension (especially the former), to which the diabetic is susceptible, there is no sound basis for attributing these lesions to atherosclerosis or hypertensive disease. My own observations substantiate those of others § which clearly indicate that the characteristic vascular lesions in the retina and glomerulus can occur in the absence of localized or generalized atherosclerosis and have no etiologic relationship to the arteriolar lesions of hypertension.

2. *Venous Stasis.*—Elwyn [29] has promulgated the view that, in some unknown manner, dilatations of the retinal capillaries occur secondarily to venous stasis, with contraction of the artery above, a condition which he calls "prestasis." This author further postulated that as a result of stasis the reduced capillary blood flow leads to anoxia of the capillary wall, through which red cells, hyalin, and lipids permeate. It is true that diabetic retinopathy is often associated with venous stasis, and not infrequently with venous occlusion. The retinal capillary aneurysms observed in cases of venous occlusion in nondiabetics and experimental animals [7] may have some bearing on this point.

3. *Duration of Diabetes.*—Although a direct correlation between the severity of the diabetes and the intensity of the retinopathy cannot be demonstrated, there appears to be some relationship of the duration of the disease to the onset of capillary lesions in the retina and glomeruli. According to Duke-Elder [30] and Wagener and associates,[28] the "diabetic age," not the chronologic age, is the dominant factor. Seventy-six per cent of their patients less than 30 years of age with retinopathy had had diabetes for at least 10 years. From this it would appear that whatever factor, or factors, cause the capillary lesions in diabetes are absent or inactive enough during the first five years to produce damage and that commonly 10 or more years elapse before definite retinal changes are discernible. Dolger [19] reported retinopathy in every patient with diabetes of some years' duration, regardless of age at onset or severity of the diabetes. Thereupon he concluded that the duration of the disease, not the method of treatment, is the vital factor in the development of these lesions.

§ References 16, 17, and 28.

It would appear at first glance that the striking increase in the frequency of retinopathy in diabetics is a natural result of the prolongation of life made possible by insulin. In my opinion, since a large proportion of diabetics over the age of 60 have normal retinas, retinopathy cannot be explained simply by the increasing longevity of the patients which followed the discovery of insulin.

4. *Increased Capillary Fragility.*—Many authors investigating diabetic retinopathy have noted an increased capillary fragility, which, in the absence of a blood dyscrasia or vitamin C deficiency, is acceptable evidence of a lowered resistance of the capillary wall.|| Beaser and associates [31] were among the first to report that increased capillary fragility was more prevalent in diabetics with retinopathy, was most frequent in the fifth and sixth decades, and occurred in 100% of the diabetic patients with hypertension. The close association between retinal lesions and increased capillary fragility is illustrated by 127 diabetic cases of long duration (10 to 29 years) reported by Root, Sinden, and Zanca.[32] In this series increased capillary fragility was demonstrated in 90, or 71%, of those with retinopathy. Rodriguez and Root found increased capillary fragility more closely related to the duration of the diabetes than to the chronologic age of the patient. In many cases, when increased capillary fragility alone was observed, this sign was followed within a moderately short period by the development of retinopathy and albuminuria. Of 321 consecutive patients reported by Beardwood, Roberts, and Trueman,[33] 46% showed increased capillary fragility and 24% retinal change. It is interesting that the patients with Kimmelstiel-Wilson disease showed the most marked capillary fragility of any of those studied and that in one patient who died with uremia the capillary fragility was so great that the Göthlin index could not be read. Cases are encountered showing marked retinopathy and normal capillary fragility; others, increased capillary fragility and no retinal pathology.

If the concept that retinopathy is due to increased capillary fragility is valid, then any therapy which improves or restores the integrity of the capillary wall should prevent further lesions and probably aid in the absorption of the lesions already present. The therapeutic use of vitamin P in retinopathy is predicated on its action in maintaining normal capillary permeability. Various drugs have been tested for their effect on capillary permeability.

In 32 cases Barnes [35] found little improvement in either capillary fragility or diabetic retinopathy. Root,[32] Peck,[36] and Beardwood,[33] and their collaborators reported similar experiences, i. e., improvement in capillary fragility after treatment with antifragility drugs without any change in the course of diabetic retinopathy. In a recent study of 10 diabetics given 180 mg. of rutin daily for three months and similar patients given a placebo, Frericks and associates [37] reported no change in either the capillary fragility or the retinopathy. Beardwood and associates expressed a hope that more satisfactory results might have been obtained if rutin and hesperidin had been prescribed in earlier stages of retinopathy. Levitt and associates [34] conclude that any retinal improvement seen with this drug is no more than can be expected when good diabetic control is maintained without rutin.

While it is by no means certain that increased fragility of skin capillaries reflects a corresponding dysfunction of retinal capillaries, the findings noted above certainly

|| References 8 and 27, and others.

point in that direction. There is at least a possibility that the lesions in the retina and glomerulus are part of an alteration in the capillary wall present throughout the body. At present this finding of altered capillary permeability remains the best evidence that the retinal and glomerular capillaries are joint manifestations of a general capillary abnormality. Still, nothing more definite can be said than that patients with diabetic retinopathy show a much higher percentage of increased capillary fragility than those without retinopathy or than nondiabetic persons of the same age.

5. *Relationship Between Retinopathy and Neuropathy in Diabetes Mellitus.*—Wagener, Dry, and Wilder [23] observed a 25% incidence of neuropathy in their diabetic patients showing retinopathy, as compared with 8% in a control series. To explain these findings, they postulated analogous lesions in the retina and the peripheral nerves. In the light of our own studies,[38] it is difficult to envision a pathogenic connection between these two conditions. We believe that neuropathy is interrelated with the as yet unexplained intrinsic metabolic changes of uncontrolled diabetes. As will be shown below, it is unlikely that, despite their high incidence in this disease, retinopathy and intercapillary glomerulosclerosis are caused directly by metabolic aberrations of the diabetic process. In my opinion, neuropathy and the vascular lesions of retinopathy both have a high incidence in diabetes and merely overlap.

6. *Relationship of Retinopathy and Intercapillary Glomerulosclerosis to the Diabetic State.*—Because retinopathy has been observed to progress rapidly in uncontrolled diabetes from the aneurysms through the stages of exudate and hemorrhage to retinitis proliferans, the condition is usually considered a complication of the disease. Moreover, the occurrence of retinopathy and Kimmelstiel-Wilson disease in young patients, with otherwise normal retinal vessels, strongly suggests that some diabetic factor predisposes to these lesions. The finding of intercapillary glomerulosclerosis in dogs made diabetic by injections of pituitary extract have been interpreted by some authors as evidence that glycosuria is specific.¶ Under the impression that retinopathy and intercapillary glomerulosclerosis are neither helped nor prevented by good diabetic control, some authors have looked upon these lesions as an integral manifestation of the basic disorder, or, as Mirsky [40] has stated it, "an associated concomitant of the disease."

By contrast, Ashton # and others * hold that these vascular lesions are much more likely to be found in persons who, for one reason or another, have experienced prolonged periods of poor diabetic control and recurrent ketosis. Whereas most observers report the appearance of retinopathy from the 10th to the 15th year of diabetes, the lesions, nevertheless, have been observed much earlier, sometimes as early as the 5th year, in patients who have flagrantly disregarded diabetic management.

Conversely, Grayzel and Warshall [42] observed that none of their juvenile diabetic patients whose control was considered good developed detectable vascular

¶ References 21, 24, and 39.

References 5 and 6.

* References 35 and 41.

lesions, even though they had the disease for 10 to 28 years. From an analysis of their data, Keiding and associates [43] concluded that control of diabetes over the years is more important than any other known factor in preventing retinopathy and nephropathy. No patient with excellent control had more than minimal eye changes. These authors found an extraordinary correlation between the degree of diabetic control and the development of nephropathy. None of 11 patients with excellent control, and only 1 of the 50 with good control, had nephropathy.

It is important to point out that the visible retinal lesions may be completely reversible, and some authors † claim they clear up with good treatment. O'Brien and Allen,[4] in six diabetic patients under 31 years of age, observed that retinopathy disappeared after two months of good control. The reversibility of retinal lesions is further illustrated by Sherrill's report [45] of a 26-year-old woman with diabetes of 18 years' duration in whom myriads of aneurysms were noted in the course of a pregnancy. Upon termination of the pregnancy at the eighth month, diabetes came under control very quickly, and, within a month, only a minimum number of red dots could be seen. Sherrill has observed other instances of severe, uncontrolled diabetes in which aneurysms disappeared after good control.

The unique finding of the disappearance of vascular lesions in the eyes in a case of diabetes with Simmonds' disease, reported recently by Poulsen,[46] provides indisputable evidence that hemorrhage, and even waxy exudates, may be curable. So long as the possibility exists that the lesions may disappear spontaneously, any appraisal of the effect of diabetic treatment on retinopathy and glomerulosclerosis must be made with caution. Although some authors ‡ hold that retinal hemorrhages tend to disappear spontaneously, the fact that early aneurysms have been seen to disappear when diabetes is controlled should be sufficiently encouraging to impress upon us the importance and the efficacy of diabetic regulation.

The investigations of Heinsius and his co-workers [48] at the Umber Hospital, Berlin, indicate that the etiology of retinopathy is not explained satisfactorily by any metabolic products or by-products of diabetes, such as acetone, creatinine, uric acid, pyruvic acid, or lactic acid. Therefore, these authors were forced to conclude that the retinal involvement in diabetes is a primary process. One clue to a possible mechanism for the development of capillary lesions in the fundi and glomeruli is McManus' [13] observation of a pink-staining polysaccharide in these vessels.

Although some authors are resigned to the idea that retinal and glomerular lesions are inevitable in the course of diabetes mellitus, in my opinion, such a gloomy outlook is not altogether warranted in the face of other observations, including our own.§ Martensson and Pal, for example, found a 40% incidence of retinopathy in their diabetic material. Six of 18 patients who developed diabetes before 20 years of age survived 22 years without retinopathy, and one patient did not develop retinopathy until after 26 years of diabetes. In a later series, 10 of their patients had survived diabetes at least 25 years without fundus changes, and 1 had had

† References 32 and 33.

‡ Reference 47. Tolstoi, E., in discussion on Root, H. F.: Complications and Sequelae of Diabetes: Relation to Control, Panel Discussion, 12th Annual Meeting of the American Diabetes Association, June 8, 1952.

§ References 1 through 4.

diabetes 34 years. In two of Peck's juvenile cases [36] the diabetes had extended well over 20 years without the patients' showing any demonstrable retinal, renal, or other vascular damage. It is conceivable, of course, that subclinical injury to the capillaries may occur in every case of diabetes, but, if so, in many cases it is clearly insufficient in degree to give rise to visible lesions. The above observations indicate, and I concur, that a patient with well-controlled diabetes can go through a normal life span with minimal retinal and glomerular changes. After the glomerulosclerosis has developed, the prognosis is poor, and the only treatment, if any, is prophylactic, i. e., rigid control of diabetes.

7. *Role of the Corticosteroids in Pathogenesis of Retinopathy and Intercapillary Glomerulosclerosis.*—A new approach to an understanding of the pathogenesis of retinopathy and glomerulosclerosis has been provided as a result of the experimental production of the Kimmelstiel nodules in rabbits by administration of cortisone.‖ Rabbits, first made diabetic with alloxan and then given hormone treatment, showed not only the renal lesions described by Rich but also microaneurysms closely simulating the lesions observed clinically in diabetic retinopathy. Previous attempts to produce these lesions with alloxan alone had been unsuccessful. Recently, retinal lesions were observed by the Johns Hopkins Hospital group ¶ in two patients taking corticotropin, a possible indication of a relative excess of cortisone and corticotropin in diabetic patients with retinopathy and Kimmelstiel-Wilson lesions. Upon reexamining the adrenal gland of a series of previously autopsied diabetic patients, lipid changes were observed in the zona fasciculata. Of 64 patients with Kimmelstiel-Wilson lesions, only 12% showed vacuoles in the zona fasciculata. Although similar changes in the adrenals can be produced by a number of factors, these findings are, nevertheless, suggestive.

Corroboration of the above-mentioned findings by adrenocortical function studies in the living diabetic patient is the next logical step. Eversole and associates observed that patients without diabetic retinopathy evinced a fall in the eosinophile count after the administration of cortisone but failed to react to corticotropin. On the other hand, a positive eosinophile response to corticotropin was observed consistently in patients with diabetic retinopathy. These observations raise questions as to a possible role of the adrenal corticosteroids in the production of retinopathy and glomerulosclerosis. If this is true, how would the diabetic state predispose a patient to such an adrenocortical effect?

According to Hinkle and Wolf,# stressful life situations may be associated with a fall in glucose and a rise in ketones, an effect which is exaggerated in diabetic patients. The histories and daily experiences of diabetics bring out many apparently spontaneous fluctuations in their symptoms and insulin requirements which coincide with important episodes in their lives. Their behavior under stress, attitudes toward food, and feelings toward their parents are often so consistent that these authors are led to interpret such psychologic manifestations as part of the total disease process.

‖ Reference 22. Rich, A. R.: Johns Hopkins Hospital Clinical-Pathological Conference, February, 1952.

¶ Eversole, S. L.: The Kimmelstiel-Wilson Syndrome, lecture given before the American College of Surgeons Physicians, April 25, 1952.

References 49 and 50. Hinkle, L. E., Jr., and Wolf, S.: Changes in Blood Glucose in Response to Stress and Their Relevance to Diabetes Mellitus, 12th Annual Meeting of the American Diabetes Association, June 8, 1952.

Biochemically, the glucocorticoids, one of which is cortisone, are related to decreased fibroblast formation and inhibit inflammation and healing. Opposing this action are the mineral corticoids (desoxycorticosterone and 17-hydroxy-11-desoxycorticosterone, Reichstein's compounds), which are related to electrolyte balance and increased formation of connective tissue, hyalin, and fibrin. The alarm reaction causes an increased secretion of adrenocorticotropic hormone (corticotropin), which then stimulates increased secretion of corticoids from the adrenal cortex. Corticosteroids alter the permeability of capillaries and thus influence the passage of water and electrolytes through these vessels. A disorder in the balance of the corticosteroids might then also be responsible for altering the permeability of the rather delicate retinal capillaries. In stress situations the diabetic action of the anterior pituitary, a much more potent one than the adrenal factor, cannot be ignored.

A report, such as a case of Cushing's disease studied by Conway and Stark,[51] to the effect that therapy with corticotropin limits the development of granulation tissue and fibrous tissue lends strong support to the view that adrenocorticosteroids may play an active part in the formation of capillary lesions in diabetes. It is significant that young persons with a slight Cushing's syndrome reportedly show a typical diabetic retinitis proliferans.[48]

In diabetes mellitus we are dealing with a profound metabolic disturbance affecting the metabolic functions of many organs and tissues, resulting in a state of imbalance of the pancreatic, anterior pituitary, and adrenocortical hormones. The aberrations may be transitory or more prolonged, depending upon the persistence and severity of the metabolic derangement. Since few diabetic patients, even with the assistance of insulin and diet, can respond at all times in a completely physiologic manner to insulin, food, exercise, etc., metabolic deviations from normal must be expected. From this it would follow that retinopathy and glomerulosclerosis are caused not alone by lack of insulin, but, beyond this, by the predominance of the pituitary and/or cortical hormones. In this sense it is logical to infer that the closer the approximation of the diabetic's state to normal, the more desirable it is and the less likely is he to suffer qualitative and quantitative metabolic changes leading to endocrine imbalance.

Of particular significance are the drop in insulin requirements and blood sugar level reported in cases of previously severe diabetes and the rapid downhill course of patients dying of renal insufficiency. May these cases not represent the end-stages of adrenal insufficiency? If the original stress reaction persists in a body no longer able to adapt to the stress, exhaustion and death result.

How to prevent or retard retinopathy and intercapillary glomerulosclerosis in diabetes is still a problem and a challenge, and after the lesions have occurred there are no satisfactory methods of treatment. In patients with retinopathy attention should possibly be given to some means of curtailing pituitary or adrenocortical activity.

The thoughts presented herein can be summarized by saying that the literature and experimental studies support the hypothesis that retinopathy and glomerulosclerosis of the diabetic may be caused by some disturbance in adrenocortical function induced by the diabetic metabolic aberration.

CONCLUSIONS

1. Diabetic retinopathy is a separate, discrete, readily recognized entity unrelated to atherosclerosis.

2. Diabetic retinopathy and Kimmelstiel-Wilson disease are closely related anatomically and physiologically.

3. In diabetics the control of the diabetes is an important factor governing the development of retinopathy and intercapillary glomerulosclerosis.

4. Diabetic retinopathy is reversible.

5. The retinal and glomerular lesions can be produced experimentally in rabbits with alloxan-induced diabetes by the administration of cortisone and corticotropin.

6. Diabetic patients showing Kimmelstiel-Wilson lesions in the kidneys present in a high percentage of the cases lipid vacuoles in the zona fasciculata of the adrenal glands.

7. Most likely retinopathy is a consequence of a metabolic disorder characterized by an hormonal imbalance.

8. The concept of adrenal hyperactivity to explain the occurrences of retinopathy and intercapillary glomerulosclerosis in diabetics, though inviting, is still hypothetical and awaits confirmation.

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COTTON FIBRILS IN THE ANTERIOR CHAMBER AFTER SURGERY

ROBERT J. BROCKHURST, M.D.
BOSTON

VARIOUS types of foreign material may be introduced into the eye during intraocular surgery, for example, talc, cilias, rubber, and cotton lint fibrils. Vail [1] recently reviewed this complication and reported three cases of cotton lint in the anterior chamber. In most of the cases of lint reviewed, as well as in Vail's three new cases, the foreign material was not deleterious to the eye. However, in some instances transient postoperative iritis occurred. Vail felt that the lint in his cases came from the air circulating in the operating room. He suggested several measures by which the amount of dust in the air might be reduced.

It is the purpose of this paper to report four additional instances of fibrils in the anterior chamber. It is believed these fibrils were cotton threads which had broken off from the cotton sponges used during the operation.

REPORT OF CASES

CASE 1.—A 38-year-old woman with mild endothelial dystrophy and bilateral posterior cortical cataracts underwent intracapsular extraction on the left eye. Healing was uneventful, and three weeks later a similar procedure was carried out on the right eye. The right eye healed without undue corneal edema,* and there were no signs of iritis. However, a large tuft of fibrils was noted in contact with the temporal iris pillar, the anterior hyaloid membrane, and the back of the cornea (Fig. 1). One month after operation fine pigment deposits were noted on some of the fibrils. Vision was 20/20 with aphakic correction. Six weeks after operation the fibrils, previously noted to be in contact with the endothelium, now were adherent at a point in the 9:30 meridian, about 3 mm. from the limbus. Around this point there was minimal endothelial edema. Motion of the temporal iris pillar would move the mass of fibrils, but the adherence to the back of the cornea could not be broken. During the next three and one-half months the appearance of the fibrils and the cornea did not change; the eye remained quiet without any signs of inflammation, and vision remained normal with correction.

When the fibrils were first seen in the right eye, further study of the left eye, which had been operated on three weeks previously, revealed a fibril lying on the hyaloid membrane. The fibril measured about 1 mm. in length, was slightly curved, and showed no pigmentary deposition on its surface. The underlying vitreous appeared normal. Six months after operation, the left eye was still quiet, and the white fibril remained unchanged and unpigmented.

CASE 2.—A 39-year-old man was operated upon for an intraocular magnetic foreign body which had perforated the cornea and lens, lodging in the vitreous behind the lens. The foreign body was brought into the anterior chamber and removed through a limbal incision, an iridectomy being done at the same operation. Following surgery there was moderately severe iritis.

* In each eye the cataract had been tumbled with an erysiphake. In each instance, there was corneal edema lasting two days.

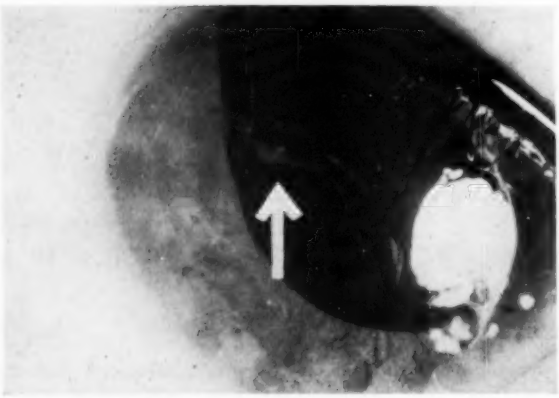

Fig. 1 (Case 1).—Photograph, taken four months after cataract extraction, showing cotton fibrils in the anterior chamber.

Fig. 2.—Tip of cotton sponge made from short-fiber cotton.

Fig. 3.—Cotton fibrils in saline.

Three days after the operation three white curved fibrils were seen adhering to the lens capsule in the region of the perforation. After six weeks the inflammatory process subsided, the eye becoming white, without cells or aqueous flare. The white fibrils showed some pigmentary deposits, giving a beaded appearance. Seven months after operation the eye was white and quiet, the fibrils still showing some pigment deposits. The lens changes had progressed.

CASE 3.—A 20-year-old man was operated upon for an intraocular foreign body, which was localized in the ciliary body, just behind the root of the iris. A traumatic cataract was present, with signs of siderosis. After removal of the foreign body, linear cataract extraction was done. The eye healed rapidly with minimal signs of iritis, which cleared after one week. Five days after operation a single curved white fibril was noted lying on the posterior capsule. Another single fibril was noted at 1 o'clock projecting from the corneal operative wound into the anterior chamber, this fibril being about 1.5 mm. long. Four weeks after operation the fibril which had been adhering to the posterior capsule was found to be absent, it having been seen the preceding day. It had apparently become dislodged spontaneously. The eye has remained quiet for a seven-month period, the fibril in the wound having remained unchanged. Corrected vision is 20/30+4.

Fig. 4.—Tip of cotton sponge made from a longer-fiber cotton.

COMMENT

In this small series of four eyes, only one showed marked postoperative inflammation (Case 2). It is difficult to assess the role of the fibrils as a possible cause of this reaction, since the original severe injury and the surgery may well have been the basis. In all cases the status of the eyes was excellent after six months.

In each operation, cotton balls, moistened in saline and rolled firmly between the palms to form cigar-shaped sponges, had been used. The cotton used to make these sponges was of a short-fiber, or staple, quality. Sponges made from such short-fiber cotton balls showed many fine fibrils of cotton projecting from the surface (Fig. 2). These fibrils could easily be wiped or broken off. Figure 3 shows cotton fibrils from such short-fiber cotton in a test tube of saline. The appearance of these fibrils is similar to that in Figure 1.

A long-fiber cotton ball, similarly rolled out to form a sponge, shows fewer projecting fibrils, and there is less tendency for these to wipe off (Fig. 4).

SUMMARY

Four eyes are described in which cotton fibrils were noted after surgery. In all instances the presence of the cotton fibrils was not injurious.

The origin of the cotton fibrils was felt to be the short-staple cotton sponges used during the operation. The use of a longer-staple cotton for such sponges is suggested.

62 Basset St., Lynn, Mass.

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CONOVER-SPAETH MAGNETIC CAMPIMETER

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AND
EDMUND B. SPAETH, M.D.
PHILADELPHIA

THIS NEW instrument was exhibited during the 1953 Session of the American Academy of Ophthalmology and Otolaryngology. The instrument was developed through the mutual efforts of one of us (E. B. S.) as a physician and the other (W. G. C.) as a patient.

The instrument was worked out to obtain more complete accuracy in central field examination. At the same time, the determination can be done in much less time than is usually required for this examination with similar tangent screens.

The instrument is 24 by 24 in. (60 by 60 cm.) with a fixed central fixation point. A magnet moves the test object freely upon the visible field. At the conclusion of testing for each radius the test object is withdrawn from view behind a concealment

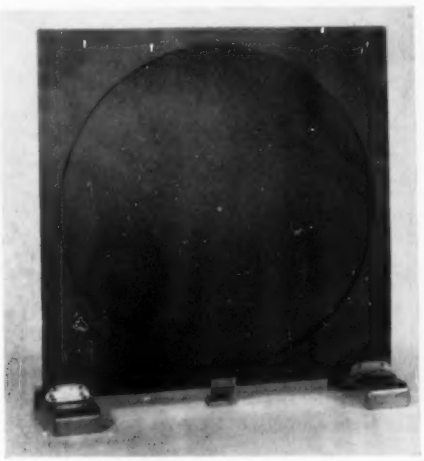

Fig. 1.—Patient's side of the instrument.

shield. At the rear, or operating, side there is a sheet of nonmagnetic metal with a circular opening which serves as a track for a bridge that spans the opening and rotates about the axis of the central fixation point. The magnet, which presses against the posterior face of the field, moves through an open channel that is calibrated upon its face. The magnet assembly, with a knob on the face of the bridge for moving it along the opening channel, has an index pointer to show the precise position of the test object, in meridians and degrees, as these appear on the front field of the instrument.

The position of the eye is 10½ minutes from central fixation. The usual head and chin rest is to be used with the instrument. This instrument is intended for use with the standard Berens chart, so that no additional office records are needed.

In operation, the physician or technician rotates the bridge to the desired radius, which is clearly indicated on the perimeter of the circle, and slowly moves the magnet knob along the channel to the desired radius, bringing the test object from concealment toward fixation.

When the patient indicates that the test object is in his field of vision, the position of the object, radius and degree of isopter, is noted on the bridge index and entered upon the Berens chart. The test object is then withdrawn into concealment and the next radius for testing selected, right or left, as is desired. The operator looks directly over the top of the instrument into the patient's eye, this being less than 24 minutes distant, and he can immediately detect any withdrawal from fixation.

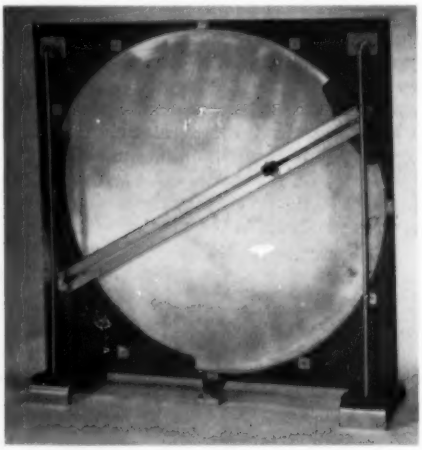

Fig. 2.—Posterior, or operator's, side of the instrument.

That the target is mechanically controlled, without the necessity for the placing or withdrawal of markers, permits a field examination with absolute accuracy and with a great saving in time.

Figure 1 illustrates the patient's visible side of the instrument. The circle marks the field of concealment. Figure 2 is the posterior, or operator's, side of the instrument. The channel, as marked in degrees, shows the knob for moving the test object. The radius being tested is indicated at the edge of the circle. Illumination is to be used as arranged by the physician—from above, behind the patient, and at an angle of about 45 degrees.

The instrument is manufactured and distributed by George P. Pilling & Sons Co., Philadelphia.

1930 Chestnut St. (3) (Dr. Spaeth).

VOLTAGE STABILIZER AND GROUND-TESTING UNIT FOR USE WITH ELECTRONIC INSTRUMENTS

S. I. ASKOVITZ, M.D.
PHILADELPHIA

THE READINGS on many types of electronic measuring and recording instruments may be significantly altered by fluctuations in the voltage of the power supply. Inadequate grounding is another frequently encountered difficulty in the use of electrical devices. That such factors must be considered, especially in work of a research nature, where accuracy is important, has been pointed out previously for the case of the electronic tonometer.*

Voltage stabilizer and ground-testing unit.

There has been developed at this laboratory a combined unit for standardizing tonography records which will maintain a stabilized voltage to within 0.5% (satisfactory for most medical purposes) and will also provide a simple test for the adequacy of an external ground connection (Figure). A voltmeter on the front panel indicates either the incoming voltage or the stabilized output, and an ammeter shows whether the current load of the attached instruments is excessive. (It may also serve to demonstrate whether the attached instrument is operating properly.) The necessary fuse protection, pilot lights, and switches are included.

This work was made possible by a grant from the Weinstock Fund.

From the Ophthalmology Research Laboratory (Dr. I. H. Leopold, Director), Albert Einstein Medical Center, Northern Division.

* References 1 and 2.

In use, one begins with all switches turned to the off position. After the plug is attached to an ordinary outlet (alternating current only), the main off-on switch is turned on. The voltmeter should indicate somewhere between 100 and 130 volts A. C. Next, the ground clip is attached to a water pipe or any metallic plumbing fixture, and the ground-testing push-button is depressed. If the external ground connection is satisfactory, the corresponding pilot light will light up. If not, another grounding site must be tried, until a proper one is found. The current load of the attached instrument may then be checked by temporarily turning on the ammeter switch. After this, the stabilizer switch may be turned on.

The electronic tonometer is plugged into either of the two sockets provided on the unit, and the ground connection of the instrument is attached to the terminal post, above. An additional socket is provided for the use of auxiliary electronic equipment, such as an amplifier in automatic tonography recording.

The voltmeter indicates at all times the voltage at the output sockets, i. e., the voltage being supplied to the electronic instrument in use. However, with the voltage stabilizer switch in the off position, the output voltage will equal the incoming voltage, and the voltmeter will read the unaltered line voltage coming from the power receptacle.

The voltage stabilizer and ground-testing unit is being manufactured by Medico Instruments, 1220 N. Broad St., Philadelphia.

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A NEW PREPLACED CORNEOSCLERAL SUTURE

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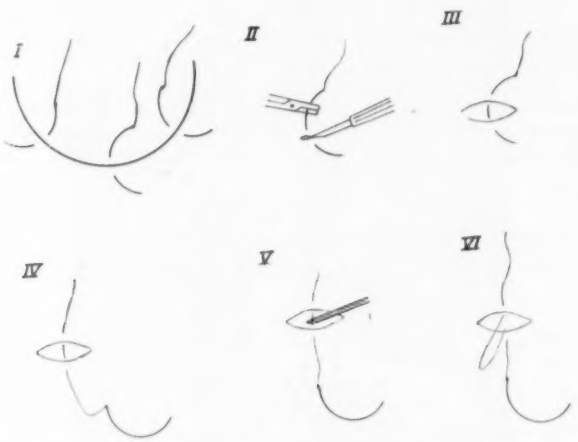
NEW ROCHELLE, N. Y.

THE SUTURE which is here described is a preplaced corneoscleral suture, being inserted at the limbus before any incision is made. It can be used either with or without a conjunctival flap. One or more sutures may be used in any part of the limbal area. I prefer three sutures, at 10:30, 12, and 1:30 o'clock.

The eye is prepared in the usual manner for cataract surgery, and the globe is steadied with fixation forceps. A 7 mm. Grieshaber needle attached to a 000000 nonabsorbable surgical (silk) suture is inserted near the limbus in the cornea, pene-



I: A 7 mm. Grieshaber needle is inserted near the limbus in the cornea, penetrating about one-third of the corneal thickness. About 2 mm. of corneoscleral tissue should be included in this bite, with the needle emerging in the sclera. The needle is not pulled through but is left in the tissue, with both the tip end and the eye end protruding.

II: The eye end of the needle is now grasped with a needle holder. With a replaceable Bard-Parker blade, a 2 mm. incision in the middle of the bite is made transverse to the needle in the corneoscleral tissue.

III: The incision is carried down to the needle, until the needle is well exposed.

IV: The needle is pulled through, and the suture is seen lying in the incised area.

V and *VI*: A loop of the suture is pulled out with a hypodermic needle or any sharp-pointed instrument.

trating about one-third of the corneal thickness. About 2 mm. of corneoscleral tissue should be included in this bite, with the needle emerging in the sclera. The needle is not pulled through but is left in the tissue, with both the tip end and the eye end protruding (Figure, *I*). All the needles, one or more, are inserted in the same manner before proceeding to the next step.

From the Ophthalmological Service of the Montefiore Hospital, New York.

The eye end of the needle is now grasped with a needle holder in order to insure firm fixation of the needle. With a replaceable Bard-Parker blade, a 2 mm. incision in the middle of the bite is made transverse to the needle in the corneoscleral tissue (Figure, *II*). The incision is carried down to the needle until the needle is well exposed (Figure, *III*). The needle is now pulled through, and the suture is seen lying in the incised area (Figure, *IV*). A loop of the suture is pulled out with a hypodermic needle or any sharp-pointed instrument (Figure, *V* and *VI*). The same procedure is carried out with the other needles which were previously inserted. From this point the operation proceeds in the same manner as after the usual preplaced suture. I prefer to make a keratome incision between the two strands of the loop at 12 o'clock and then to extend it with scissors.

This suture has certain advantages over other sutures. Its insertion is easy and should present no difficulties to the occasional operator. On the first attempt, other surgeons and I carried through the procedure with ease. All the needles are inserted before any incision is made, so that there is no danger of inadvertently entering the anterior chamber with the cutting instrument, and thus being forced to place sutures in a soft eye. The apposition of the edges of the wound is exact, as to both depth and radial approximation.

Baldino,[1] in 1935, described a suture technique which is somewhat similar to this one. He inserted the needle in the limbal area and left it there. He then cut down on the needle and dissected around it, so that he entered the anterior chamber. When the anterior chamber was opened, he pulled the suture through. Any subsequent suture, by this technique, would be placed in a soft eye. Dissecting around the needle to enter the anterior chamber presents difficulties which the suture I have described does not.

650 Main St.

REFERENCE

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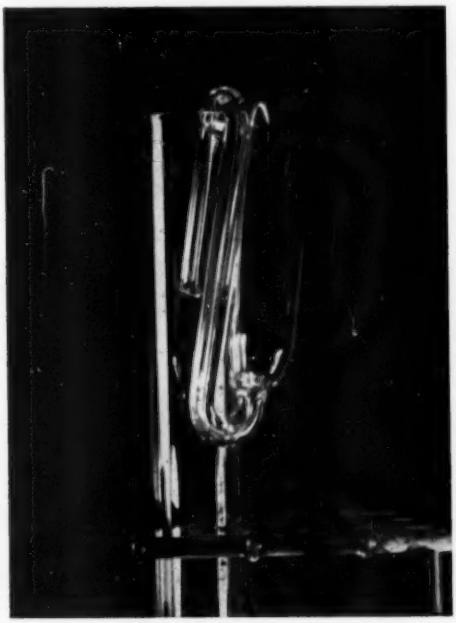
APPARATUS FOR CHEMICAL EXTRACTION OF SMALL PIECES OF CORNEA

HAROLD L. KERN, Sc.D.
BOSTON

THE SIMPLE apparatus shown in the Figure has been found eminently satisfactory for exhaustive extraction of cornea with aqueous solutions. It was developed after we had been unable to find a suitable extractor described in the literature. It has been employed in determining cations in corneal stroma after exposure to various alkalis. The extractor should prove useful in assaying dissolved or bound ions or uncharged molecules in any small sample of firm, permeable material which



Apparatus for chemical abstraction of cornea.

is not disintegrated by the extracting medium. Rapid and near-quantitative removal of individual portions of solvent is possible with a minimum of manipulation.

A 1 mm. bore capillary is sealed to the end of a 70 mm. length of 14 mm. I. D. Pyrex tubing and bent in the shape shown in the Figure. A "dimple" may be made just above the capillary to prevent plugging.

In our particular application, the exposed tissue (0.1 to 0.5 gm.) is blotted dry and placed in the extractor, and 1.0 and 2.0 ml. of 0.1 N HCl is added. After one-half to one hour at room temperature the extract is forced over to the larger collecting test tube by air pressure (e. g., by blowing into the chamber through a rubber tube and stopper). This process is repeated until no further ions are extracted. Four to six extractions suffice for removal of alkali cations from corneal stroma.

From the Howe Laboratory of Ophthalmology, Harvard Medical School.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

CONJUNCTIVAL DERMOID WITH MARKED SEBORRHEIC COMPONENT

WHILE dermoids of the conjunctiva are occasionally seen in the practice of ophthalmology, there are certain features of the case herein described which make it of more than usual interest.

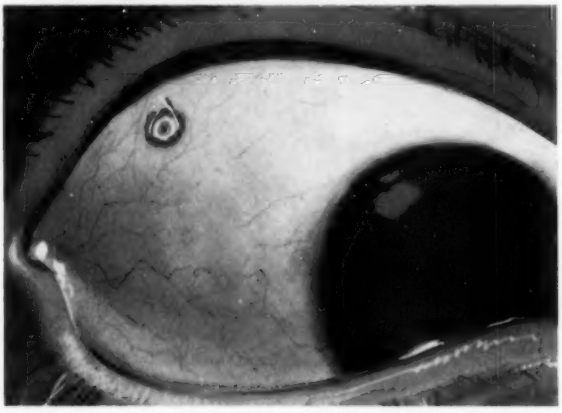


Fig. 1.—Gross view of conjunctival lesion.

On Feb. 2, 1953, Mrs. E. O'G. a 32-year-old white woman, was seen for the first time. She gave a history of "a cyst in the right eye which had been bothering off and on for 16 years." Further questioning revealed that the onset of her ocular difficulty antedated her menarche by just a few days. The subsequent episodes of irritation antedated each menstrual period by two to three days and seldom occurred at other times or, as she recalled, during her single pregnancy. The irritation she described consisted of a conjunctival injection accompanied by a white, oily secretion.

On inspection, a moderate amount of this secretion was noted in the right conjunctival sac and was oily, as she described. There was noted, also, a slightly elevated whitish-yellow, well-circumscribed lesion, 4 mm. in diameter, in the bulbar conjunctiva high in the superior fornix

on the temporal side (Fig. 1). From a central opening, slightly less than 1 mm. in diameter, a small amount of the secretion could be expressed. There were several short blond hairs growing about the opening and over the entire surface of the lesion.

The lesion was excised en bloc. The pathologist's report indicated "adenoma sebaceum" of normal, but misplaced skin.

Fig. 2.—Section of conjunctival dermoid, showing conjunctival epithelium, hair follicle, sebaceous glands, and collecting duct.

The sections (Fig. 2) showed a profusion of sebaceous glands about a central collecting duct lined with stratified squamous epithelium, numerous hair follicles, and normal conjunctiva.

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Annual Reviews

STRABISMUS

Review of the Literature

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NEW YORK

AGAIN THIS year it has been my aim to cover the world literature on strabismus for 1953; however, no claim to completeness can be made. Everything that could be found and translated has been included, although in some instances abstracts have had to suffice. Many articles that do not actually add anything new have been reviewed because they tell what people in other parts of the world are thinking and doing about strabismus.

The outstanding event in the field of strabismus during 1953 was the publication, by the American Academy of Ophthalmology and Otolaryngology, of the symposium on strabismus, held at the annual meeting in October, 1952.[1] Following the precedent established by the other symposia that have been given by the Academy in recent years, this was not merely a series of papers on one subject. Six of the leaders in this field labored for two years, traveling back and forth across the country in order to spend many days in meetings until they had found fundamental truths on which all could agree. Thus, the symposium represents the mutual conclusions of these six experts and therefore offers the finest conceivable statement of basic principles that our present knowledge will permit. No attempt will be made to review the volume (it is only 56 pages) because it is my conviction that everyone who is practicing or intends to practice ophthalmology should study it carefully.

Another important event was the appearance of the fifth edition of "Gifford's Textbook of Ophthalmology," by Adler.[2] No one should be misled, as I was when the completely rewritten fourth edition was published, in thinking that this is only a textbook for medical students, as the author implies in his preface. The chapter on disturbances of ocular motility is the finest introduction to the study of this subject that I know of. It should be carefully read by all residents in ophthalmology, and many of the older ophthalmologists will derive much benefit from it.

BINOCULAR VISION

The problem of how an object may be perceived as single when it is viewed with both eyes is not solved, as Asher [3] points out. To reexamine du Tour's opinion that there is no fusion of two images, but that always one of a pair of corresponding points is suppressed, he devised 12 exercises on the stereoscope, on which he based the following observations: The correspondence of retinal elements is completely rigid and unchanging. One of a pair of corresponding points always suppresses the other. When there is contour, the suppressing power of retinal elements on each side of it is enhanced. When there is disparity of contour, the retinal elements on both sides of this contour in one eye will suppress corresponding points in the other eye. If the extent of the suppression is smaller than the disparity between the contours, diplopia occurs but depth perception is possible. If the extent

of the suppression is greater, one contour is suppressed and single vision occurs with depth perception. The contour of one part of the image may be dominant in one eye and that of another part may be dominant in the other eye. Asher's final decision is to advance the theory that one of a pair of corresponding points always suppresses the other.

Peripheral Fusion.—Declaring that he agrees with Burian's work on peripheral fusion, Winkelman [4] reports further investigation of it, using Polaroid projectors in a darkroom. 1. Dissimilar images were presented to the foveas. This did not cause fusional movements because they could not be combined in a single mental image. 2. Small vertical lines, one above the other, were projected for the foveas, and larger, dissimilar peripheral images were projected 40 cm. from the center, on both nasal or both temporal retinas. The foveal images were displaced but not enough to bring peripheral images on corresponding areas. The displacement decreased with repetition. This is a primitive reaction of the retina to light stimuli, probably a congenital and unconditioned reflex.

Anomalous Correspondence.—Anomalous correspondence continues to be a major problem from the points of view of pathogenesis, diagnosis, and treatment. There is still much difference of opinion among those who have studied this phenomenon. Two important contributions have come from Copenhagen. Rønne and Rindziunski [5] define anomalous correspondence as any alteration of the normally fixed binocular sensorial relationship. This could be criticized as being too broad a definition. They believe that anomalous correspondence is an adaptive phenomenon. In addition to the usual methods of making the diagnosis, they suggest several variations. The after-image test is done with the filament presented vertically to each eye; this may show separation when there is a cross by the usual method. They repeat the test at different distances and get considerable variation; the angle of anomaly is usually smallest at 6 meters. In the "prism rack after-image" test a horizontal prism rack is moved quickly up and down; the distance between the after-images may change, indicating a change in correspondence. This may be the only test to show that normal correspondence is beginning to break. In the "prism-rack Maddox-rod" test the red streak should move but sometimes does not, indicating a change in sensorial correspondence. Based on clinical evidence, the authors find a close parallelism between the development of anomalous correspondence and macular suppression. Comparing intermittent and constant squint, they found the following significant differences that imply a different etiology for the two groups:

	Normal Correspondence by After-Images	Simultaneous Perception with Small Pictures	Age of Onset
Intermittent squint	73%	45%	3 yr. 3 mo.
Constant squint	30%	7%	2 yr. 1 mo.

They have divided the abnormalities in sensorial relationship in squinting patients into five stages, the prognosis becoming worse with each stage:

Stage 1 (very early phases of squint): Normal correspondence, suppression to prevent diplopia and confusion; diplopia with Worth dots or Maddox rod. Haploscope: alternate macular suppression with very small pictures; normal perception with fusion pictures; stereopsis. After-images: normal, but tendency for parallel negative images to separate in prism rack test.

Stage 2: Alternate suppression with Worth dots; Maddox rod normal. Haploscope: suppression with medium or large pictures; no stereopsis. After-image: normal correspondence with positive crossed images; negative crossed images may be abnormal; parallel images usually abnormal; angle of anomaly small and changing. (It is probable that most of us would not call these first two stages anomalous correspondence.)

Stage 3: Suppression with Worth dots; diplopia with Maddox rod, the subjective angle being smaller. Haploscope: no simultaneous macular perception; cross-over on subjective angle; suppression scotoma larger; subjective angle considerably smaller than objective. After-image: abnormal with crossed positive image; angle of anomaly increasing but usually inconstant.

Stage 4: Suppression with Worth dots; small subjective angle with Maddox rod. Haploscope: simultaneous perception, with large pictures at subjective angle close to zero; fusion at subjective angle. After-image: usually anomalous correspondence with nearly constant angle of anomaly.

Stage 5: Slight suppression with Worth dots; harmonious anomaly with Maddox rod. Haploscope: simultaneous perception with small pictures, subjective angle near zero; fusion easy with some amplitude. After-image: always anomalous with constant angle identical with objective angle.

The authors believe that this classification represents a continuous evolution of anomalous correspondence. The patients frequently pass through these stages in reverse in therapy.

These same authors discuss the pathogenesis of anomalous correspondence in their second paper.[6] They conclude that anomalous correspondence can best be explained as a sensorial adaptation to the altered position of the eyes, serving as a solution to otherwise paradoxical perceptions. The evolution of anomalous correspondence is perhaps mediated through hypothesized transverse couplings between the two layers of ganglion cells, separated by the white line of Gennari, characteristic of the striate area in the occipital cortex. The anomaly should consequently be regarded as one of perception and the adjective "retinal" omitted. Anomalous correspondence is of the greatest importance for the clinician because it prevents a functional cure. The cure of a firmly fixed anomalous correspondence is extremely difficult; consequently, the prophylaxis, which implies early treatment, is our only effective therapy.

Following Verhoeff's teaching, Jaffe[7] prefers to call anomalous correspondence "anomalous projection." He believes that we have either normal correspondence or noncorrespondence. He describes the following test for anomalous projection: Expose one eye to the vertical bar of light for 20 seconds; then cover the exposed eye. If there is correspondence, the subject will see the after-image with the previously occluded eye. If there is noncorrespondence, the unexposed eye is not aware of the after-image. This was true in all 71 patients with noncorrespondence. Jaffe believes this method to be the most sensitive and simplest test for correspondence. His explanation of this test is not convincing. He does not tell whether the after-image seen by the occluded eye is positive or negative; it would have to be positive. One wonders whether suppression might not explain the absence of the after-image in the occluded eye.

Jaffe found the following incidence of noncorrespondence in strabismus:

Monocular esotropia 37% of 86 cases
Alternating esotropia 87.5% of 32 cases
Monocular exotropia 25% of 12 cases
Alternating exotropia 50% of 16 cases

He is unable to explain the high frequency of unharmonious anomalous projection. The age of onset is the most important factor in the development of anomalous projection. His treatment follows traditional lines. Operation is indicated in early cases and may be all that is necessary. Preoperative orthoptic training is a waste of time but is used postoperatively in all children under 9 years.

Four basic principles for the treatment of anomalous correspondence in squint are given by Castanera Pueyo.[8] 1. Avoid inhibition of the macula of the squinting eye. Occlusion, either monocular or alternating, is very important until bimacular stimulation is possible, by means of orthoptics or surgery. 2. Avoid simultaneous stimulation of the macula of one eye with the peripheral retina of the other, by occlusion. 3. Attempt simultaneous stimulation of the two maculas to regain similar projectional values, using orthoptics or surgery. 4. Produce parallelism of the visual axes to attain permanent and spontaneous binocular stimulation.

A novel approach to the treatment of sensorial disturbances is suggested by Hamburger.[9] He recognizes two types of squint, which correspond to two types of binocular vision: (1) the type of active competition, in which both foveas are striving for dominance, and (2) the type of inactive competition, with one eye the dominant one. In 20 cases he was able to convert alternating squint, with anomalous correspondence, into monocular squint by occluding the nonpreferred eye for several months. The patients were then amenable to orthoptic treatment.

Fixation Disparity.—Differentiation of small degrees of esophoria and esotropia is an important and difficult problem. Gittoes-Davies [10] points out that the patients show a slight shift with the cover test, yet give binocular responses to other tests. This has been called fixation disparity by Swan and Ogle, but Jampolsky classifies it as esotropia. Gittoes-Davies selected 80 cases with the following characteristics: (1) diagnosis of slight esotropia or intermittent esotropia or esophoria; (2) manifest hyperopia of 2.50 D. or less; (3) slight amblyopia; (4) normal movements; (5) very slight esotropia, with partial recovery in the cover test; (6) angle of 5 degrees or less, unilateral foveal suppression, and slight angle of anomaly; (7) adduction of 10 degrees or more; (8) stereopsis appreciated with numbered slides; (9) appreciation of physiological diplopia. Orthoptic treatment was given in 87% of the cases to eliminate suppression and improve the fusional amplitude. Occlusion, appreciation of physiological diplopia, and bar reading were employed. Operation was advised in 70%—single recession in 50%; bimedial recession in 30%, and resection and recession in 15%. Study of the vital statistics in these cases failed to produce an explanation. Of the patients, 88% showed some amblyopia, of which 80% failed to improve. The average deviation was 10 to 15 D. for distance and 15 to 21 D. for near. The patients appeared to have normal correspondence on the synoptophore, but with great care an angle of anomaly of 2 degrees or less could be shown. Surgery reduced the deviation with the cover test but did not change the angle on the synoptophore; there was still a slightly incomplete recovery to binocular single vision.

Gittoes-Davies then discusses the various possibilities, citing the opinions of several authors. She doubts that abnormal retinal correspondence could exist in so small a deviation or that projection could be incorrect by 2 degrees or less. Good fusional amplitude and accurate stereopsis are not consistent with anomalous correspondence. She agrees with Swan and Ogle that if a patient appreciates physiological diplopia, he must have binocular single vision, consequently, the anomaly in these cases must be esophoria, not esotropia. The small angle of anomaly found on the synoptophore may be the result of incapability of refined fixation because of amblyopia. The author concludes that these patients maintain binocular single vision and enjoy all the advantages of it, in spite of a slight manifest deviation; that it is not a true manifest deviation but is fixation disparity compatible with binocular single vision. Panum's area is enlarged because of the amblyopia; these patients are able to compensate for fixation disparity up to 6 D. They should be treated as cases of phoria: (1) glasses only for visual acuity; (2) occlusion; (3) orthoptic training for fusional amplitude and objective convergence; (4) operation to reduce the maximum dissociated deviation, and (5) postoperative orthoptic training. She emphasizes the importance of not using glasses unless they give binocular single vision.

ETIOLOGY

That the majority of the troubles in strabismus are a consequence of insufficiency of dominance of one cerebral hemisphere is an interpretation presented by Dejean, Viallefont, and Dollard.[11] Of 92 patients with strabismus, 15 were left-handed and 4 were stammerers. In the absence of hemispheric dominance, the impulses coming from the two hemispheres are badly synchronized, coordination does not exist, and the cortical elements lose their influence on the peripheral motor centers. These centers then organize themselves spontaneously to realize fixation of the better eye, or of one eye in alternators. The inward rotation of the poorer eye is the least unpleasant position, the image falling on the blind spot. This discussion is interesting theorizing, for which no real proof is offered.

Alabaster [12] offers another theory for the development of hyperopia and squint. He suggests that vitamin A deficiency in the parent, prior to mating, is a factor and that vitamin B deficiency plays a part after birth. These deficiencies are caused by a high carbohydrate diet made from refined flour. He advocates dry yeast as a national beverage (in England) to give an excellent source of protein and vitamin B. He presents no evidence to support these speculations.

Pavlov's theory of conditioned reflexes has another supporter in Chytilová-Divišová,[13] who believes that comitant squint can be explained on this basis (section on "Pathological Physiology").

Age of Onset.—Nordlöw [14] gives us another statistical study. This year he has analyzed the ages of onset in 518 cases of permanent and intermittent esotropia. He finds four possible sources of error in recording this part of the history: (1) failure to notice the squint or the exact time of onset; (2) reluctance to consult a physician; (3) lapse of memory, and (4) overrepresentation of certain age groups. He allows the patient seven years after the onset in which to seek medical aid. In 403 of his cases the esotropia was permanent and in 82 intermittent. There were more girls, probably for cosmetic reasons. The incidence was 51% during the first year, 19% during the second, 12% during the third, and 10% during the fourth. Of the

permanent esotropias, 57% appeared during the first year, while of the intermittent forms the highest incidence (23%) was in the fourth year, and 16% came on during the fifth year. These figures agree closely with those of Keiner and Scobee but disagree with those of Jonkers.

Jonkers [15] had a comparable series (504) of cases of convergent strabismus, in which only 6% were alternators. Severe amblyopia (acuity less than 0.1) was frequent when the onset was under one year of age. The refraction did not differ greatly from normal, but there was a constant slight anisometropia. The largest number had the onset between the ages of 1 and 2 years, and in most the strabismus had appeared before the third birthday.

PATHOLOGICAL PHYSIOLOGY

In his de Schweinitz lecture, Adler [16] approaches the pathological physiology of strabismus differently than in his previous writings on this subject, and gives as well the result of an important experiment. After stating that stabismus is a disturbance of ocular motility due to a number of separate and unrelated pathological processes, some of which are unknown, he divides the neuromuscular mechanism into (1) the supranuclear portion (upper motor neurone) and (2) the nuclear and infranuclear portions (lower neurone). The pathways for both voluntary and reflex movements can be divided into these two portions. Any lesion involving a lower neurone will give incomitant strabismus, while those of the upper neurone will affect the two eyes equally, causing gaze paralysis if versions are affected or comitant strabismus if vergences are involved. Comitant strabismus is always innervational in origin—either excessive convergence or insufficient divergence innervation.

In an attempt to settle the dispute as to the existence of a divergence mechanism, Adler and his associates conducted the following experiment: Insulated bipolar electrodes were inserted into a normal lateral rectus. The changes in electrical potential and the number of impulses discharged per second in varying positions of gaze were recorded. In divergence from the convergent position, there was a burst of impulses which preceded the actual movement by milliseconds, showing that the electrical activity produced, and was not the cause of, the eye movement. These experiments prove that during divergence from the convergent position the lateral rectus muscles are actively innervated. Divergence is due, therefore, to cocontraction of the lateral rectus muscles, with simultaneous inhibition of the medial rectus muscles. A divergence mechanism therefore exists.

This experiment would have been even more convincing if the same electrical activity could have been shown during active divergence, as when overcoming a base-in prism.

Adler goes on to inquire how pathological processes disturb the vergence mechanism and produce comitant strabismus. Tonic convergence is normally excessive in childhood. Poor vision in one eye is followed by esotropia because of failure of the optomotor reflexes. Refractive errors produce strabismus by adding the effect of accommodative convergence for distance in the hyperope and lack of it for near in the myope. Slight paralysis of vertically acting muscles, sufficient to dissociate the eyes and make fusion impossible, may release excessive tonic convergence. Alcohol and anoxia cause an increase in the convergence tonus for distance. Excessive divergence impulses are probably the explanation of intermittent exotropia. Many very young children show weakness of abduction without paralysis of the lateral

recti—probably an interference with the normal divergence innervation. Some children with esotropia but no signs of cerebral palsy show evidence of damage to cortical pathways, indicating brain injury or lack of myelination. It is a source of great amazement that this author, who has written so much on this subject, has been able to produce another paper with a fresh point of view and new material. The evidence that he offers for a divergence mechanism is of primary importance.

A different classification of concomitant strabismus is offered by Urrets-Zavalia.[17] He divides his cases into three types: 1. Ophthalmoplegic type: early onset, usually due to a vertical imbalance and accompanied by serious sensorial anomalies. The possibilities of a functional recovery are very poor; orthoptic training is generally ineffective; surgery is only cosmetic. 2. Anisesthetic type, due to disparity of retinal images. The prognosis depends on the possibility of correcting the disparity. Surgery and orthoptics may also be useful. 3. Primarily accommodative type. Early total correction of the ametropia is essential. The sensorial disturbance may be overcome with relative ease.

The electroencephalograms of seven children with squint were examined by Pesme and Faure.[18] All showed similar EEG anomalies indicating hyperexcitability of the mesencephalodiencephalic structures. The authors believe these results indicate neurophysical disturbances associated with strabismus (section on "Amblyopia").

Hiroishi [19] reports the "electro-oculogram" in 22 cases of strabismus, before and after surgery. As this article was available only as an abstract, it was impossible to know exactly what electro-oculography is, but apparently it is an electrical way of recording eye movements. In strabismus caused by hypofunction of one muscle, there is a lowering of the velocity curve in movement of the corresponding eye away from the center and toward the direction of the corresponding muscle contraction. The decreasing leg of the position record appears gently sloping. In cases of hyperaction, there is an increase in the velocity curve and a gentle sloping of the ascending leg of the position record. The author concludes that the electro-oculogram is valuable in analysis of the nature of the strabismus.

AMBLYOPIA

The whole subject of amblyopia in relation to strabismus has continued to occupy a prominent place in the current literature. A very complete review of the history of the treatment of amblyopia has been given by Hefel.[20] After pointing out that the exact site of the loss of vision in amblyopia ex anopsia has not yet been determined, Parsons-Smith [21] suggests that the disorder is an active inhibitory process in the cerebral cortex and that the electroencephalogram may throw some light on its mechanism. He studies the EEG's of 50 patients with amblyopia between 5 and 12 years of age. Twelve records were normal; 7 were doubtful, and 31 were grossly abnormal. Thus, a high proportion of children being treated for amblyopia have severe EEG abnormalities. These disturbances of cortical rhythms support the thesis that abnormalities are present in the central nervous system in amblyopia associated with strabismus. They indicate that the cerebral cortex is functioning abnormally and tend to support Keiner's theory of delayed myelination. From the EEG appearances, it is possible to select those children who are likely to be disturbed by orthoptic training, so that they may be treated appropriately.

In a second article, Parsons-Smith [22] reports that it is possible to alter the normal electrical activity of the cerebral cortex by illuminating the retina with a flickering signal. Fifty children with strabismus and amblyopia were subjected to flicker stimulation at various frequencies. Four varieties of responses resulted, of which two were new and probably directly linked to the process of visual extinction. In the majority, the cortical response was the same regardless of which eye was stimulated. This evidence supported Wald and Burian's conclusion that in amblyopia the entire apparatus of light perception and spatial localization is normal, whereas that part subserving the highest function of pattern vision is defective. In a smaller group, the responses were different, and perception of light was involved, in addition to a defect in pattern vision. When the sound eye was stimulated, responses were obtained over both hemispheres, while no response was evoked when the amblyopic eye was stimulated. The light signal appears to be modified in certain amblyopic children either by diffuse cortical lesions directly connected with the affected eye or by more discrete lesions within the pathways from that eye.

While discussing electroretinography in general, Burian [23] points out that the responses obtained in eyes with amblyopia ex anopsia vary with different patients. If the visual acuity is rather low, one may find that the occipital cortex may respond with rhythmic discharges to rhythmic light stimulation of the normal eye, while it may fail to do so when the amblyopic eye is stimulated. In cases in which the visual acuity is not too low, photic driving may be elicited from the amblyopic eye but the amplitude may be less than when the normal eye is driven. The central transmission time may be prolonged in comparison with that on stimulation of the normal eye.

Using the method of transfer of after-image from the fixing fovea to the amblyopic eye, described last year by Brock and Givner, Jaffe and Brock [24] have made further studies of amblyopia. They find that amblyopic eyes fix eccentrically and that there is a direct relationship between the depth of the amblyopia and the degree of eccentricity. With the same test, they were able to demonstrate small central scotomas in most amblyopic eyes with eccentric transfer. They distinguish between amblyopia with eccentric fixation and amblyopia ex anopsia. Best results are obtained from occlusion therapy in the latter. Occlusion will probably fail when the eccentric retinal area is fixed and there is an absolute central scotoma. Improvement may be expected when the scotoma is very minute and the eccentric area is not fixed. Amblyopes who retain central fixation respond well to occlusion at any age. This method would appear to be an excellent way in which to study small degrees of eccentric fixation.

Bourquin [25] defines unilateral amblyopia as visual acuity below 0.8, and at least 4/10 below the other eye. He found 457 instances of amblyopia (all types except toxic amblyopia) in 34,000 cases. In 189 it was associated with strabismus. In this last group, acquired diseases occurred with equal frequency in the amblyopic and in the nonamblyopic eye.

One of the most provocative contributions to appear in 1953 was Bangerter's 96-page monograph on the treatment of amblyopia.[26] In it he describes the set-up of his *Sehschule* at St. Gall (Switzerland), in detail. All forms of amblyopia are treated at the school, but for this review we shall be confined to those accompanying strabismus, although these make up the majority of the cases. In founding the school, 10 years ago, he purposely disregarded the literature on amblyopia to avoid

preconceived ideas. He has delayed this report on his methods until he is sure of the results. He defines amblyopia as weakness of sight without organic defects, or with a defect out of proportion to the degree of weakness—a disproportion between visual faculty and expected visual function. Amblyopias with strabismus are divided into three degrees: high degree (acuity lower than 0.1); medium degree (0.1 to 0.3), and slight degree (0.3 to 0.8). The high-degree amblyopias are further subdivided into (1) those without fixation, (2) those with paracentral fixation, and (3) those with approximate central fixation. Bangerter stresses the importance of amblyopia in terms of occupation in later life and believes the incidence is between 1% and 2% of the general population. In discussing the etiology of amblyopia, he cannot accept the suppression theory. He feels that the success of treatment, other than occlusion, argues against it. He concludes that the cause cannot be stated.

For testing vision, Bangerter uses the illiterate E's (*Pflüger'schen*) on a chart on which they can be rotated, individually. He seldom gets an accurate test in a subject under the age of 4 years. The distance between the test letters has a close relationship to the visual acuity. He has devised two instruments on which the distance between the test letters can be varied, horizontally on one and in all directions on the other. These test "ability to separate"; this ability is deficient in amblyopia and is susceptible to training.

Bangerter calls his institution a "pleoptic" school, which means an institution that embraces the entire field of amblyopia. "Pleoptic" therapy is the term for the treatment given at the school. This treatment can only very briefly be summarized: 1. Creation of the most favorable visual conditions possible: (*a*) The sharper the image, the sooner it will be observed. He undercorrects hyperopia of 0.5 D. and overcorrects myopia of 0.5 D. If the strabismus calls for full hyperopic correction, he gives it only to the good eye. Glasses should be prescribed only when it is certain they can fulfill a purpose. (*b*) A deviation of more than 35 degrees makes treatment impossible; in such a case early unilateral operation is advised. 2. Intensive stimulation of macular vision by adequate stimuli. These stimuli must be adapted exactly to the nature and degree of the amblyopia. 3. Exploitation of the interrelations of central and peripheral vision. Fatigue of the retinal periphery facilitates increase of macular function when there is paracentral fixation. 4. Exploitation of the interrelations of the two eyes. Visual impressions of the good eye can be used for the weak eye through memory. 5. Drawing on the other sensory organs: touch and hearing. 6. Exploitation of optic engrams (memory). 7. Training of ability to separate. A large number of original instruments have been devised to carry out these various steps, and they are described in detail.

While this monograph is not intended as a guide to the treatment of amblyopia (we are invited to visit the school for that), it gives the steps of Bangerter's program in considerable detail. It is my impression that, in addition to employing many new methods, this program is far more elaborate than any other that has come to my attention. The only treatment employed during the first two years is instillation of atropine, 0.5%, every other day in the fixing eye, three out of four weeks. During the third and fourth years, short regular exercises of the amblyopic eye are carried out. Occlusion is avoided. Real training is begun after the age of 4 years. Basic training consists of training the eye for central vision. Passive stimulation, chiefly with lights under carefully controlled conditions, comes first. Then active stimulation is employed, using the "acoustic localizer." This is carried out for two half-hour

periods daily for an average of three to six weeks. The principal training is carried on when a high degree of amblyopia has been overcome, progressing through the various steps, as mentioned above. Full occlusion is used only in clinical treatment after the visual acuity is 0.2 to 0.3, primarily to strengthen central fixation. Orthoptic training is begun as soon as the visual acuity is 0.4. (Bangerter defers the discussion of orthoptic training for a later publication. Meyer [27] was impressed with Bangerter's school but found that the orthoptic work in Switzerland was far less advanced than his treatment of amblyopia.) Meyer emphasizes early treatment but realizes that it is possible to start too early and that cooperation is essential. The optimum age for training is between 6 and 9 years. Children are given a trial run of 10 sessions; if there is no progress, training is stopped and tried again later. The training is continued as long as progress is being made.

Except for the school idea, the most radically different part of Bangerter's treatment of amblyopia is his handling of the cases without fixation or with paracentral fixation. In spite of his repeated condemnation of the use of complete occlusion by Anglo-Saxons, it is primarily in these cases that he really objects to its use. If he had looked into the literature a little more thoroughly, I believe that he would have found most writers in agreement on this point. However, it is also true that most of us do not try to treat these patients, and here he has offered something definite, although he admits that he still succeeds in only a small percentage of this group. Incidentally, he admits that when "pleoptic" treatment is not available, occlusion is justified and is effective in many cases.

This monograph may prove to be exceedingly important. Bangerter has definite convictions about the treatment of amblyopia and has had extensive experience to back them up. He has had a number of original ideas that, as he describes them, would appear to have real value. He is obviously extremely ingenious, as evidenced by the numerous original instruments that he has devised. It is impossible to evaluate his results for the data given, but his presentation is impressive. He undoubtedly is working very hard to do something with amblyopia. An American is left with a number of questions and some doubt. Imagine being able to put amblyopia patients in an institution for three weeks! We might be able to buy the equipment that he recommends, but where would we find room for it in our crowded hospitals? Even worse, where would we get the trained personnel to carry out the treatment? Therefore, while the program that he describes sounds like a very real advance, it is doubtful whether it could be rapidly adopted in this country.

Other writers are also concerned about the patients who do not have central fixation. Bagshaw [28] teaches central fixation on the synoptophore, using colored targets, before starting occlusion. The ultimate prognosis for binocular vision is governed by the age of onset and the duration. If there is a definite history of squint since birth, the chance of developing useful acuity is small. Every effort should be made to get good visual acuity in each eye, even if binocular single vision cannot be achieved. Observing that children with eccentric fixation are severely handicapped by total occlusion, Swenson [29] advocates occluding the temporal half of the glass in front of the amblyopic eye (to cover the corneal reflex), thus excluding stimuli to the nasal retina. This gives both passive and preventive treatment of anomalous correspondence. She finds a reduction in the suppression area in four to six weeks, a change in the character of fixation, a decrease in the angle, and an increase in the visual acuity. This is the most commendable form of original think-

ing, and we should all be grateful for a constructive approach to these difficult problems. Unfortunately, others who have tried this treatment have not had much encouragement.

An occluded lens that can be graded to reduce the visual acuity of the better eye one or two Snellen lines below the amblyopic eye is described by Olmsted.[30] She uses it to treat suppression after the eyes have been straightened by surgery.

The case of a pair of monozygotic girl twins who had identical squints but who reacted differently to identical surgery and to occlusion is presented by Ryerson and Calahan.[31] These different responses lead the authors to conclude that occlusion is not hopeless if the first attempt fails and that there may be an optimum time for each patient.

EXAMINATION

Variations in the after-image test for anomalous correspondence have already been discussed. With few exceptions, the other new material on examination is concerned with modifications of the red-green test. Arruga [32] has devised a transilluminated screen which is used with Lancaster or Foster torches. He believes that it combines the advantages of the Hess screen and the Lancaster test. Halbron [33] wonders why the Hess method is used so little in France. Believing that one reason is the difficulty of getting and keeping complementary colors, he describes the Lancaster test and new equipment that is now available in France. In discussing this paper, Hugonnier criticizes the new apparatus because it does not project streaks. He advocates calling it the Hess-Lancaster test, as it combines the best features of both. In a second article, Halbron, Paquet, and Correard [34] describe a case of hyperphoria in which the diagnosis was made by this test and the muscle to be operated was indicated.

Foster [35] prefers the Lancaster to the Hess test except in the method of recording it. He uses a streamlined Hess diagram on a board. He first plots the diplopia with a white light; then, using colored torches, he plots the deviation with the patient, first using the green torch, then the red. The same diagram is stamped on the patient's record, and both primary and secondary deviations can be charted on the same diagram. He points out that the Hess test is useless in long-standing paretic squint, complicated by alternating suppression. The Lancaster method will record it, but if there is abnormal retinal correspondence it records the subjective angle. Weidmann [36] also criticizes the Hess screen because of the difficulty of getting and keeping complementary colors. He also finds that the short working distance produces too much convergence and that some patients have difficulty in handling the wand. He has devised a "tropometer" in which nine green lights are projected on a Hess screen. The patient wears red-green glasses and uses a red torch. The test is usually used at 2 meters, so that there is no stimulation of accommodation or convergence. An added advantage is that the lights can be projected on the ceiling in examining a patient in bed.

Believing that ocular paralysis is frequent as the origin of strabismus but finding the diagnosis often difficult, especially in young children, Leurent [37] emphasizes the importance of precise measurement of the vertical element. He relies on the following tests: 1. Hess or Lancaster: This gives a comprehensive picture; the patient is not asked to explain his responses; the test is rapid but is difficult to interpret in complex cases. 2. Synoptoscope: This can measure vertical divergence at the

same time as the horizontal deviation, in nine positions; it is more accurate than the Hess test; it can be used when there is deep macular suppression. 3. Cheiroscope: It is easy and rapid; cyclophoria is more easily diagnosed, permitting immediate differentiation of an oblique and a vertical rectus paresis; it gives a sort of photograph of the positions of the images (Smolik[70]).

ACCOMMODATIVE STRABISMUS

Accommodative strabismus receives special attention in Volume 9 of the *British Orthoptic Journal*, there being six articles on this subject. Apparently, this was not planned. Throughout these papers, cases of this strabismus are divided into two groups: (1) typical accommodative squint, in which the glasses fully correcting the hyperopia remove the deviation for both distance and near, and (2) atypical accommodative squint, in which the glasses correct the deviation for distance but there is still excessive convergence when the subject is making an effort to see at close range. While I have been aware of these two groups, this division into typical and atypical is new to me. Robinson[38] found the age of onset earlier in the atypical type and suggests that the overconvergence for near may be a developmental habit that became fixed before proper glasses were given. But some of the atypical patients were not neglected; all had visual acuity within one line and very little suppression. Robinson's theory for the development of the atypical cases is that there is a weakness or underdevelopment of Müller's portion of the ciliary muscle, which then requires excess innervation of accommodation for close work; this condition, in turn, causes overconvergence by way of the frontal reflex. This tends to inhibit the development of the normal harmonic reflex, so that production of the normal range of convergence may become impossible. Added plus spheres for close work, from the onset, are the most satisfactory treatment; they may be gradually reduced and eliminated. She is the only one to give Costenbader credit for his pioneer work with these "atypical" cases and to use bifocals for their treatment.

Dissatisfaction with the theory of accommodative squint and the many failures is expressed by Lloyd.[39] He has found no mention of subnormal accommodation in the literature. After citing some of the usual objections and expressing doubt as to the existence of suppression, he offers a new theory. Two factors are postulated: (1) transient weakness of the ciliary muscles, and (2) lesions of one or both optic nerves, causing reduction in central vision. Some weakness of the lateral recti and a definite paralytic vertical component are likely. He assumes that these are caused by some minor, unrecognized disease that had a transient action. The reduction in the power of the ciliary muscle causes excess innervation, so that the accommodation-convergence relation is disrupted. The reduced central vision interferes with the development of fusion. He believes that too much emphasis is placed on refraction; full correction tends to reduce the visual acuity and will retard the full development of the ciliary muscles. The hyperopia should be fully corrected only at the onset to help the weakened ciliary muscle. Early operation, before the age of 5 years, has given the best results. This theory is an interesting one, but no proof is offered.

A group of cases of accommodative squint is surveyed by Fitton.[40] She divides them into recent cases and those discharged a number of years ago. The recent cases can be divided into two groups: (1) those in which the patients learn to

accommodate easily without converging and have good binocular visual acuity without glasses, and (2) those in which the patients are unable to accommodate without convergence and have poor binocular visual acuity that never improves. The age of onset is earlier in the second group and the hypermetropia is higher (Dowler [41]). Fitton suggests that in this group the accommodation squints developed before the harmonic reflex and the child took an early interest in close objects. When the two groups were given the same dissociation treatment, the subjects in the first group responded immediately, while those in the second failed to respond. She found that the patients discharged some years previously had acquired good binocular visual acuity, as the result of a large number of treatments. This may be due to a decrease in the hypermetropia, to orthoptic training at the onset, and to development of the harmonic reflex.

Trying to find the difference between typical and atypical cases, Dowler [41] analyzed 170 cases with ages between 3 and 14 years. Seventy-nine of her cases were classified as atypical. In these cases there was less hyperopia (Fitton found the opposite in a smaller series), a greater interval between onset and glasses, and a possibility of preexisting heterophoria, because more showed an esophoria with glasses and the Maddox rod. Only a few of them showed improvement with orthoptic training. A defect of relative accommodation is suggested. In 20 of these atypical cases good results were obtained from a recession of one medial rectus muscle.

Parsons [42] objects to the term "atypical." She believes that the squint in these cases is just as physiological as the "typical" accommodative squints, being due to inadequacy of the harmonic accommodation-convergence reflex. Surgery is not the cure for a physiological defect. These cases "come right in time." The age of complete recovery is usually at 12 or 15, but may be as late as 17, years of age. Orthoptic exercises to teach relaxation of accommodation are recommended. It is of interest that Parsons has never used bifocals in these cases.

In discussing the significance of accommodation in orthoptic treatment, Stewart and Vaughton [43] find that faulty binocular relative accommodation is the chief trouble in the cases referred to their clinic. Esotropia is intermittent at first. If given prompt attention, it becomes accommodative; if not, binocular vision, once broken down, cannot be regained but unequal accommodative effort develops in the two eyes. This may lead to anomalous correspondence. The original upset should be relieved by full correction; this will straighten the eyes and prevent suppression in the majority of cases. The authors suggest keeping the patient atropinized for a time at the onset, to get full relaxation. This complete relaxation of the ciliary muscle is the only way in which to prepare a child for orthoptic training and the development of bifoveal fusion.

Dobson [44] discusses refraction in relation to the treatment of very young squinters and presents some interesting ideas. She defines squint as a motor symptom of disorganization in the nerve fiber pathway of the oculomotor system, resulting in an unbalanced innervation between antagonistic muscles. She finds a purely spastic squint commonest during the first three years, caused by convulsions, colic, fright, anger from frustration, and toxins from childhood diseases. She does dynamic retinoscopy at 13 cm. and finds a high (positive) shadow in these cases of spastic squints. In accommodative squint, there is a comparatively low shadow, due to

hypertonicity. Her normal refraction figures are as follows: 1-2 years, +0.50 D.; 3 years, 4.00 D.; 4 years, 3.00 D., and 12 years, 1.50 D. The refraction of the fixing eye progresses normally, but the squinting eye retains a high (positive) shadow. She does not give the full correction because the function of accommodation has been inhibited. She discusses the treatment under four headings: 1. Attention: The squinting eye must be made to fix; the object must be interesting. 2. Occlusion: Vision should be permitted only on the temporal side of each eye; this encourages independent action and correct movement, produces rapid alternation, and prevents suppression. Total occlusion will regain only that amount of vision that existed before the deviation commenced. Total occlusion does not benefit abnormal retinal correspondence; rather, it stabilizes the perverted binocular vision. 3. Bead trainer, to stimulate vision in the squinting eye. 4. Version training with the myoflexor.

Miotics.—A number of American ophthalmologists have at last accepted Abraham's work on the use of miotics in the treatment of strabismus; so two new articles by this author are of considerable interest. He [56] finds that in cases of strabismus with anisometropia a miotic in the more ametropic eye is useful. He believes that most cases of convergent strabismus have an accommodative factor and that accommodation may be a factor regardless of the refractive error. The amplitude of accommodation may be different in two eyes with equal visual acuity at 20 ft. (6 meters). He uses miotics in the amblyopic eye for stimulation of the accommodation. He is convinced that miotics give greater coverage than glasses. He has used miotics for seven years, in some cases without detrimental effects. Diisopropyl fluorophosphate (Floropryl) has been used in over 300 cases, and as long as four years, with no untoward effects.

In a later article, Abraham [57] describes general reactions in two children who were being treated with diisopropyl fluorophosphate. In one case, in which 0.01% was used nightly in one eye, the child became nauseated and began to wet the bed; he seemed to stagger, yawn, and stretch. A second child, on the same dosage, developed a nervous tic and throwing back of the head. The symptoms disappeared when the drops were stopped. A word of caution, when using such a powerful drug, is certainly in order; however, one might question such bizarre reactions in two out of the large number of patients he has treated. Of considerably more interest and importance are the iris cysts that appear around the pupillary margin in some cases, even when only 0.005% diisopropyl fluorophosphate is used. He considers these cysts an indication for modification of the treatment; however, they tend to disappear when the drops are stopped.

CONVERGENCE INSUFFICIENCY

Convergence insufficiency was the subject of the symposium at the combined meeting of the American Orthoptic Council and the American Association of Orthoptic Technicians in 1952. As is usual with such symposia, this one gave an excellent summary of our present knowledge of the subject without adding much new material. The physiology of convergence is reviewed by Fink.[45] He can find no agreement as to a definition of convergence insufficiency and believes that the etiology is not clearly understood. He concludes that convergence insufficiency is an inadequate convergence due to a deficiency of fusional convergence and feels that it would more appropriately be called fusional vergence insufficiency.

The classic picture is described by Capobianco,[46] and the examination of patients with this disturbance is given in detail. She emphasizes the importance of the accommodation effort syndrome. The medical treatment, from the physician's point of view, is given by Simpson.[47] He places great emphasis on the use of loose prisms and finds that such exercises almost never fail to bring relief from the asthenopia remaining after correction of the refractive error. He gives detailed instructions for these exercises. Healy [48] discusses the orthoptic treatment, emphasizing the importance of the psychological approach. She gives the details of home exercises and the orthoptic routine and offers the ophthalmologist an outline for treatment: white pin and red filter; prism bar and flash light; physiological diplopia and bar reading; Orthofusor and stereoscope. The objective should be 60 △ of prism convergence and a near point of convergence of about 20 mm. The prognosis is excellent in all selected cases. In summarizing the symposium, Burian [49] stresses the behavior of vergence movements, especially for near, as the most important factor. The treatment is based on developing these vergence movements in response to disparate stimulation.

INTERMITTENT EXOTROPIA

One of the most significant papers to appear in 1953 was that by Knapp [50] on intermittent exotropia, because it gives the most satisfactory explanation of the development of this condition that has been found, as well as a logical approach to the treatment. Knapp prefers this term to divergence excess because it is descriptive, without any etiologic implication. After discussing the four theories of etiology and finding some value in each, he presents a working hypothesis: The child is born with an abnormally divergent position of rest, which the author prefers to call the "position of inattention." This may be atavistic. If the divergence is large, it may be noticed early. If small, it may not become apparent until asthenopic symptoms appear, much later. When convergence develops (at 3 months), the exotropia decreases. In most cases it remains stationary for many years; i. e., the exotropia is abolished by voluntary or accommodative convergence. Or it may progress rapidly, owing to one or more of the following factors: (1) the divergent position of inattention becoming more marked; (2) less hyperopia than usual for the age; (3) personality, the patient being quieter and more prone to daydreaming, and (4) weak fusion. When diplopia and confusion result from malalignment, the child has two choices: (1) suppression of the image from the deviating eye, the easy way, and (2) motor fusion. There are two difficult periods in which fusion may be inadequate: that of the heavy, close work of the late teens, and that of early presbyopia. The exotropia tends to increase with time, owing to the reduction in the hyperconvergence tone of childhood, lessening of the accommodation, and increasing divergence of the orbits. The suppression is merely an extension of the normal suppression of physiological diplopia; it occurs whenever the visual axes are out of line. A secondary retinal correspondence may develop, so that there is normal correspondence when the eyes are straight and anomalous correspondence when they are divergent. The degree with which the child gives way to suppression determines the course in intermittent exotropia. 1. He gives in entirely and acquires exotropia early. Once suppression is constant, he is very refractory to treatment. 2. In the usual case the disorder remains an intermittent exotropia for distance unless there is secondary convergence insufficiency. There is remarkably deep suppression for distance but slight or none for near.

Knapp is convinced that patients with intermittent exotropia should be treated as early as possible. In the early cases, before suppression patterns are established, the patient is too young for orthoptics, so that a recession of one or both lateral recti, of 4 to 5 mm., is indicated. In the older children, from 5 years on, the suppression should be treated just before operation, but stimulation of convergence must be avoided, as it may cause the child to overconverge after operation. The training should be undertaken only after surgery is agreed upon, working at the objective angle and stressing divergence. The operation should be done only when suppression is eliminated and there is constant diplopia under room conditions. Intensive postoperative antisuppression and fusion training should be given. Once convergence insufficiency has been added, surgery should include shortening of a medial rectus plus emphasis on convergence training. The tendency to surgical undercorrection may be explained by the difficulty in getting a full measure of the exotropia. This problem has not been solved.

Humphriss [51] presents an interesting theory to explain divergence excess. He finds many points in common between vertical incomitancy and divergence excess. He believes that most cases of divergence excess have incomitancy, but that it is usually masked. Overaction of the contralateral synergist is the most marked sequel of an initial mild pathological condition and persists after the latter has cleared. There are three sequels of paresis of a right medial rectus: (1) overaction of the left lateral rectus; (2) contraction of the right lateral rectus, and (3) inhibition of the left medial rectus. After partial recovery there would be (1) divergent squint, due to overaction of the left lateral rectus; (2) divergent squint, with looking to the right, due to contraction of the right lateral rectus, and (3) slightly subnormal convergence, due to inhibition of the left medial rectus. This condition would appear on the surface to be comitant and to have all the features of a divergence excess. Basing the treatment on this theory, he has four aims: (1) to overcome suppression; (2) to establish entrenched diplopia when the eye is diverged (full details are given for accomplishing this by an exercise with two knitting needles of different colors); (3) to overcome divergence and enable the child to acquire the ability to fix binocularly at infinity, and (4) to remedy convergence insufficiency. In his experience, patients with 10 degrees or less of divergence have responded well to orthoptic training. Surgery is frequently necessary for deviations over 10 degrees. He advises, first, a recession of the lateral rectus of the deviating eye, and, second, a recession of the other lateral rectus. A resection and recession done on the same eye are frequently disappointing because a resection on the initially paretic muscle is invariably unsatisfactory, or, if done on the other eye, enough is not done to prevent the overaction.

VERTICAL STRABISMUS

Alternating Hyperphoria.—Last year, a surprisingly large series of cases of alternation hyperphoria was reported by Crone, together with his theory to explain this condition. He has now greatly expanded his discussion of this problem in a monograph of 178 pages.[52] Unfortunately, it is printed in Dutch, so that I have been limited to the author's summary in English. He points out that the optomotor reflexes have horizontal, vertical, and rotary components. Stimulation of the temporal upper quadrant and the nasal lower quadrant of the retinas gives an impulse

to extorsion; stimulation of the other two quadrants gives an impulse to endorotation. There is evidence of the existence of monocular optomotor reflexes in infants and children with convergent squint. He has enlarged his group of cases from 80 to 113. Alternating hyperphoria is accompanied by exorotation of the covered eye, while the uncovered eye is endorotated. Rotatory nystagmus is very frequent; on covering one eye, it changes to a horizontal jerky nystagmus with the fast component directed toward the side of the uncovered eye. Crone finds evidence for the theory that alternation hyperphoria is caused by an unequal development of the monocular optomotor reflexes, such that the impulses to deorsumduction, endorotation, and adduction are stronger than the opposites. Thus, the impulses from the lower nasal quadrants of the retinas are at fault. When the alternating hyperphoria is associated with divergent squint, a relative predominance of the optomotor reflexes from the upper nasal quadrants of the retinas is assumed. In alternation hyperphoria combined with convergent strabismus there is usually a hyperfunction of the inferior obliques, while in divergent strabismus it is usually the superior obliques that are overactive. He finds alternating hyperphoria in a latent form in many subjects as shown by the frequency with which alternating hyperphoria becomes manifest when binocular vision is interrupted. It has been my understanding that alternating hyperphoria and dissociated vertical divergence were different entities, with probably quite different etiology. The implication here is that the dissociated type can change into alternating hyperphoria. This is a tremendous piece of work on a complex and poorly understood subject. While Crone has not solved the problem, he has made an important contribution.

The pathogenic influence of the vestibular apparatus in the mechanism of dissociated vertical deviations is refuted by Toselli.[53] Stimulation of the labyrinth by cold or warm water and by a 90-degree inclination of the head did not produce alternating hyperphoria.

Torticollis.—Crone [54] found ocular torticollis in many cases of alternating hyperphoria. The head is usually tilted toward the fixing eye. The traditional explanation of the torticollis as a means to reestablish binocular vision in paresis of an oblique muscle does not apply in all cases. The patient does not get binocular vision; the vertical deviation is not influenced by head inclination; there is no cyclophoria, and there is often an alternating hyperphoria and congenital nystagmus. The torticollis in these cases is probably caused by a rotatory deviation of the fixing eye. This must be a pathological endorotation. It is seen much more frequently in very young children and tends to spontaneous correction.

Two cases in which the diagnosis was congenital paresis of one superior oblique, with the head tilt and a positive Bielschowsky sign, are reported by Urist [55] because after recession of the overacting inferior oblique they showed a paresis of the other superior oblique with overaction of the corresponding inferior oblique. He emphasizes the danger of the surgeon's thinking that he had overdone the first operation in such a case. After citing Bielschowsky and Adler on the pathological physiology, Urist describes another component to explain why torticollis is commoner in paralysis of the superior oblique. Normally when the head is tilted to the right, the right eye moves up and in to fix. In right superior oblique paralysis, the head tilt to the left is very effective because (1) the paretic muscle takes no part in dextrocyclotorsion of the right eye and (2) the right eye is abducted so that it is out of the field of the overacting inferior oblique.

TREATMENT *

General.—Lyle [58] gives a general survey of the orthoptic and surgical treatment of nonparalytic strabismus. He defines a cure as effected when the visual axes point in the same direction in all circumstances and binocular function is normal in all respects. A child is never too young for some form of treatment. Neglect leads to amblyopia and abnormal retinal correspondence; these are more likely to occur with earlier onset of the strabismus. Glasses are of value in three ways: (1) in improving visual acuity, (2) in reducing the angle, and (3) in restoring parallelism and normal binocular function. Occlusion is used to improve vision and to prevent abnormal retinal correspondence. Orthoptic treatment is a means of improving binocular function. It can never be used before the age of 3 years, and usually not until the child is 4 or 5. In young infants, the vision should be equalized, then the eyes set straight by surgery. This frequently leads to normal development of binocular single vision. There is little to be gained by surgery before the age of 15 to 18 months because binocular reflexes are undeveloped. There is always a chance of a complete cure in infancy if there is no pathology.

In convergent strabismus, Lyle considers five factors: 1. The hereditary factor. This calls for routine examination of the offspring of squinting parents. 2. The accommodative factor. There is always a chance for binocular single vision if the onset is after the age of 3 years. The outlook is excellent if there is normal correspondence and fusion. Slight amblyopia is not a bar to binocular vision. (The author does not like bifocals.) If the patient is 5 or over, Lyle then treats surgically, with recession of one or both medial recti. Somehow this breaks the anomalous relationship between accommodation and convergence. 3. The paretic factor. This may account for a considerable number of cases, although an obvious defect of excursion may be difficult to demonstrate. The treatment is always surgical. When the squint is associated with "up drift" of the contralateral eye on lateroversion, Lyle prefers a myectomy of the inferior oblique even when there is no hyperphoria in the primary position, as it enlarges the field of binocular fixation and improves appearance. He considers a recession more difficult, without offering any advantage. He differentiates between "up drift" and the "elevation in adduction" commonly present with large esotropias. 4. The fusion factor: some peripheral or central defect. Gross defects in unilateral visual acuity, due to an organic lesion, are consistent with normal binocular function. Lyle doubts Worth's theory of a defect of the fusion center. 5. The psychological factor. No doubt, strabismus may be precipitated by this factor in some cases, but psychotherapy is rarely helpful.

The exact result of an operation can never be forecast. Lyle considers it unwise to retroplace a medial rectus more than 5 mm. in an infant or more than 6 mm. in older children. It is unwise to try to correct more than 25 to 30 degrees on one eye. Several factors are to be considered when one is planning an operation: 1. The larger the deviation the greater the effect. 2. The more variable the angle the greater the effect. 3. If there is habitual limitation of excursion, the effect will be less. 4. If there is secondary weakness of convergence, the effect will be greater.

* It was my hope to make a continuous story of the treatment of strabismus. However, so many of the articles cover several phases of the treatment that it seemed more valuable to review them singly and then to summarize them at the end of the section. Treatment, particularly orthoptics, has already been mentioned in several earlier sections of this review.

5. The higher the hyperopia the greater the effect. 6. The longer the duration the less the effect. 7. The younger the infant the greater the effect. Lyle discusses three types of divergent strabismus: 1. Divergent strabismus that is secondary to loss of sight. This calls for cosmetic surgery. 2. Divergent strabismus that is secondary to an operation for convergent strabismus. This also is a cosmetic surgical problem, as there is always a gross defect in binocular function. This surgical correction should be conservative; it is easy to make the eye convergent again. 3. Primary divergent strabismus. As a sequel to uncorrected myopia, this is rare today. As a neuromuscular defect, it is always intermittent at first. It tends to become worse and constant. Surgery is the only cure. In these cases the eyes should be made a few degrees convergent to avoid recurrence. Preoperative orthoptics should only be used to overcome suppression.

An analysis of 550 cases of strabismus has been made by Rodriguez Barrios and Martinez.[59] They found a family history of strabismus in 40%. Obstetrical accidents and infections in early childhood were important. At least 20% had the onset at birth; there were less during the second year but more during the third, owing to accommodative strabismus. Amblyopia occurred in 34%, of which 62% had convergent and 15% divergent strabismus, and 22% had a vertical component. Retinal correspondence was tested in 292 cases, of which 50% had anomalous correspondence. In the medical treatment, the authors follow approved methods, advocating an early start with glasses and occlusion. Orthoptic training is indicated if cooperation and visual acuity are adequate, when there is orthophoria for distance from glasses and occlusion, as preparation for operation, and when a small angle remains after operation. Their steps in orthoptic training are (1) to teach the child to alternate; (2) to treat anomalous correspondence and to combat suppression, and (3) to develop fusion, with amplitude and stereopsis. Surgery is not advocated until the age of 2 years, because the authors believe that general anesthesia is then tolerated better. They give the following indications for operation in convergent strabismus: (1) after glasses have been worn for three months, if the patient is too young for orthoptics; (2) when normal correspondence is not achieved or the angle is not modified by medical treatment; (3) when the angle is greater than 20 degrees, and (4) when amblyopia is uncorrected and there is eccentric fixation; but correction should wait until the child is 12 to 15 years of age. If the child is under 10 years, operation is deferred until maximum visual acuity, normal correspondence, and fusion with amplitude are obtained, if possible. In partially accommodative strabismus, the authours operate to correct the deviation with glasses. If there is a remote near point of accommodation, they work only on the lateral recti. They grade the amount of recession, depending on the near point. If the deviation is greater for near, they do bimedial recessions. For an accompanying vertical component, they prefer a recession or a marginal myotomy of the inferior oblique, done at the same operation. They always find an intorsion after weakening an inferior oblique, which causes a change in the astigmatic axis. The horizontal correction is greater when combined with a weakening of an inferior oblique.

A gloomy picture of the present status of strabismus therapy is painted by Riise.[60] He believes that 2 to 4% of the population are squinters, that most go through life without binocular vision, and that a great many have uniocular amblyopia. The results in amblyopia are poor if the onset is during the first year and occlusion

is not started until the third year of life. Orthoptics is impractical in many countries because of the widely scattered population. He believes that prophylactic treatment is the only hope and that it must be started before the amblyopia has developed. He advocates starting occlusion as soon as there is a constant strabismus, either alternating or monocular. He gives a full hyperopic correction as soon as possible and continues alternate occlusion if the deviation is not eliminated. He operates when the child is old enough (but fails to explain when this is). If there is a residual deviation of 7 to 8 degrees, he uses alternate occlusion for three months, and then does a second operation. If the residual deviation is less than 7 to 8 degrees, prisms are prescribed. He is afraid of early operation because of the danger of a secondary deviation but realizes that he may be wrong in this. He apparently considers early operation as any time under the age of 6 years. He analyzes a small series of cases in which operation was done under the age of 6 years and, while disappointed with the results, he seems to feel that if he could get the patients earlier and give them orthoptic training he would do much better.

Another who is greatly dissatisfied with the handling of muscle problems is Ruedemann.[61] He is making a psychological study of these children because of the tendency for the foveas to revert to their previous positions and for vision not to be maintained. He has straightened the eyes, cosmetically, in 80% of his patients with strabismus, but only 10% have second-degree fusion and less than 10% have third-degree fusion. Unless the patients are carried to third-degree fusion, which is held with good amplitude, we produce neurotics with inferior intellectual abilities. He believes that inferiority complexes are secondary to lack of foveal coordination. He has been able to detect foveal coordination as early as 28 days. Twenty per cent of the preschool group show some lack of foveal coordination. The correcting mechanism must start as soon as the lack is apparent. These ideas are interesting, but no supporting evidence is offered.

Orthoptics.—Three articles from South America indicate that the principles of orthoptic treatment are well understood and are being practiced there on a high plane. Moacyr de Aguiar [62] discusses in detail the training of technicians and the proper relationship between the technician and the ophthalmologist. He believes that Brazil is now equipped for the proper training of technicians. He shows a remarkable familiarity and understanding of the British and American literature on orthoptics. The selection of cases for orthoptic training is given by Barbosa da Luz [63] and follows the accepted practice in this country. The author is a firm advocate of orthoptics as a complement to glasses or surgery. In describing the orthoptic treatment of strabismus, Wareing [64] gives in considerable detail the actual procedures on the synoptophore. Her routine appears to follow closely the latest and most approved methods. These papers are primarily of interest to orthoptists.

Moreu Gonzáles-Pola and Abraldes Puértolas [65] believe the frequency of pure primary motor defects and the vertical factor in squint have been exaggerated. The current tendency to early operation is censured because no functional cures can be expected from surgery alone and most parents refuse or give up orthoptic training after the eyes have been straightened by operation. Orthoptic training is useful in 80% of cases but not applicable under the age of 5 years. The authors oppose early surgery and favor preoperative orthoptics.

Keiner [66] makes a strong plea for beginning the treatment as early as possible, as it shortens the influence of abnormal conditions and opens the way for normal

development of reflexes. First, the abnormal reactions that have developed must be removed. Almost all cases show some amblyopia, which must be corrected. This should be done with total occlusion. He reports his results with 113 children, aged ½ to 6 years, with convergent strabismus, treated conservatively. Correction of the refractive error was the only treatment used for the alternators. Cure was obtained in 75% of the monocular cases and in 25% of the alternators, a total of 68%.

The indications for orthoptic training are considered by Hugonnier,[67] who believes that his question should be answered by the ophthalmologist rather than by the orthoptist. The treatment of amblyopia should be done by the physician, and the child should not be sent to the orthoptist until vision is almost equal in the two eyes. The prognosis is good if the onset is after 3 years but bad if before 2 years of age. He gives the following prognostic classification: 1. Strabismus of late onset receiving immediate treatment. The prognosis is excellent. (*a*) Accommodative type: Treatment with glasses, and with exercises later, should cure almost all. (*b*) Nonaccommodative type: Operation, with exercises later. 2. Strabismus of late onset but neglected. A paretic or spastic element is added with time; treatment therefore is surgical. Binocular vision has a poorer prognosis the longer the delay, but one should always try for it. 3. Strabismus of early onset. The prognosis is bad, being worse the earlier the onset. If the strabismus is congenital and is not operated on before the age of 2 years, there is no chance of binocular vision; so operation should be done before the age of 2 years, if possible. Keiner concludes that the prognosis for binocular vision is good in all cases of strabismus of late onset, but that cure will not always be obtained. There is a possibility of binocular vision in cases of early onset if the operation is done before the age of 2 years.

The importance of the appreciation of physiological diplopia is emphasized by Wehrheim.[68] She considers it one of the criteria of normally functioning eyes that must be present before a patient can be declared functionally cured. Before any attempt is made to teach physiological diplopia, the patient must have normal correspondence, steady fixation, reasonably long attention span, and fusion at some point within arm's length. Patients who suppress with straight eyes can learn to recognize suppression by the exercise she describes. The author uses it routinely in all cases of convergence insufficiency. It is valuable as a preoperative exercise. She gives the details of the procedure, with emphasis on the use at home.

An excellent article for opthalmologists, because most of us know so little about the subject, is an evaluation of home training in orthoptics by Robinson.[69] Home training is an essential phase of orthoptic training, but it depends on the binocular ability of the child. Binocular work should never be done at home when there is anomalous correspondence. The children so treated must have normal correspondence, some ability to fuse images at the angle of deviation on the major amblyoscope, and some range of fusion. The following conditions may be benefited by home training: dissociation of accommodative squint, convergence insufficiency, divergence excess, and divergence insufficiency. The details of home training are given.

Smolik [70] accepts the value of orthoptic training as uncontested but finds the modern instruments very expensive. He describes a new device. One projector projects two pictures, one red and one green, which are reflected by two mirrors

that can be rotated around horizontal and vertical axes, onto a screen. The patient wears red-green glasses. A hemispheric screen would be preferable. This same instrument could be used for examination. At the time of writing this article only an experimental model had been produced.

The orthoptic treatment of paralytic strabismus has received comparatively little attention. Thomas, Grimault, and Brocker [71] agree with Lyle's views in this matter and describe four traumatic cases (no diagnosis given) in which cure was effected by orthoptics alone. The treatment was started immediately in one case, and after three, six and seven months, respectively, in the others. Two other traumatic cases, of total third nerve paralysis, each had a recession of the lateral rectus and orthoptic training. Lateral movements were good; fusion was stable in the horizontal plane, but vertical excursions were weak. The authors conclude that if the patient has enough will and perseverence, orthoptic treatment will give better results and is excellent as preparation for surgery. In discussing this paper, Hartmann expressed the opinion that orthoptic treatment is very useful in pareses with diplopia but without deviation. He believes that it will shorten the recovery period. In older patients it can increase the field of binocular vision.

Surgical Treatment.—A very disturbing monograph on the surgical treatment of concomitant strabismus, by Parfonry and Polliot,[72] has come from France. Published as the annual report of the Ophthalmological Society of Paris, it appears to speak with considerable authority. One wonders whether it is representative of current opinion in France. The authors divide the evolution of the treatment of strabismus into four periods: (1) that from Dieffenbach to Donders, when surgery was the only treatment; (2) that from Donders to about 1920, dominated by a desire for an ideal cure and ending in great uncertainty; (3) that from 1920 to the end of World War II, dominated by the ideas of Poulard, which gave logical directions for the surgical treatment, and (4) that since the war, in which the efforts of the Anglo-Saxons to reeducate binocular vision has caused a shift back to the second period, with many of the uncertainties and contradictions. Since Poulard's teachings are little known in this country, their third and fourth periods are a distinct surprise, and one wonders whether this point of view is not uniquely French, achieved without real familiarity with the British and American literature.

It will be impossible to go fully into the arguments of Parfonry and Polliot (the monograph has 86 pages). They are opposed to early operation and favor operating at puberty, for the following reasons: 1. The eyes often become straight with growth. 2. Postoperative deviations are more frequent in younger children. 3. General anesthesia carries a danger. They are not convinced that amblyopia ex anopsia exists. Amblyopia that improves rapidly under treatment is not true amblyopia; vision was there but suppressed. True amblyopia cannot be improved. (This distinction appears to be a matter of definition.) They consider the theory of abnormal retinal correspondence to be very questionable and believe that binocular vision is not absolutely necessary. While accepting the theoretical basis for a functional cure, they are convinced that it is rarely attained.

They state that most early operations are failures, the primary strabismus either returning to the original deviation or later changing into a secondary deviation of the opposite sort. Apparently, French children are quite different from those with strabismus in this country, for the authors think that the psychological problem

caused by a squint is exceptional, if it exists at all. From the way the authors stress the dangers of general anesthesia, one must conclude that they have had serious complications, which are almost unheard of in this country.

Parfonry and Polliot advocate a controlled tenotomy alone or tenotomy combined with a muscular advancement with tendinous resection. (The operations are described.) In alternators they divide the surgery between the two eyes. They have never found it necessary to operate on the obliques. For small vertical components, associated with horizontal deviations, they shift the advanced muscle up or down. For larger vertical components, alone or combined with horizontal deviations, they prefer a controlled tenotomy of the superior rectus for hypertropia or an advancement of the superior rectus for hypotropia. After operation they bandage both eyes for 48 hours, as they feel a monocular bandage leads to diplopia. They would prefer to use no bandages, for this reason: On either the first or the second postoperative day, depending on the findings, they adjust the controlling sutures. After that no more adjustments can be made.

In conclusion, they apologize for advocating a treatment that is 25 years old—an operation in adolescence, with use of local anesthetic, which will give complete straightening of the eyes without risk to the patient, and probably without binocular vision. I find very little in this monograph with which I can agree. The authors are arguing against all our modern concepts of the nature and treatment of strabismus, and I find their arguments out-of-date and entirely inadequate. To have these completely outmoded ideas put forth in this authoritative form is indeed discouraging.

In an attempt to determine the relationship between bilateral squint surgery and postoperative incomitance, Costenbader † analyzed 289 cases of comitant strabismus. He defined incomitance as a difference of more than 10 △ in the two temporal fields. Unilateral surgery was performed in 159 of his cases, of which 77% immediately were incomitant and 64% were finally incomitant. In 39 cases unilateral surgery was followed by a similar operation on the other eye; only 23% of these were finally incomitant. Bilateral symmetrical surgery was used in 89 cases; 15% were incomitant immediately and 5% more were finally incomitant. Costenbader concludes that incomitance occurs much more frequently after unilateral than after symmetrical (bilateral) surgery. Incomitance from unilateral surgery may be overcome by performing a similar procedure on the other eye. Disproportionate surgery causes no higher incidence of incomitance than proportionate surgery (equal amount of resection and recession on the same eye). When incomitance exists, correspondence and satisfactory alignment are adversely affected, but not to the degree that one might expect. It will take a much larger series of cases definitely to prove Costenbader's thesis, but once again he is leading the way in a significant trend. His belief in the importance of symmetrical surgery is shared by an increasing number of surgeons. Bangerter [26] suggests the same idea when he states that the purpose of operation is the creation of normal rotations and rejects the attempt to attain straight eyes by means of a unilateral operation in high-degree strabismus except when it is caused by a unilateral functional disturbance.

A thorough familiarity with the British and American literature is shown by Giardini.[81] With few exceptions, he follows approved methods of treatment with occlusion, orthoptics, and surgery. He emphasizes the danger of trying to do too

† References 73 and 74.

much at one operation, with resulting limitation of motility that prevents binocular vision. Instead, he prefers several moderate procedures, done separately. He relies on recessions and resections but no longer does both operations on one eye at the same time because of the danger of overcorrection.

Foroni [75] describes the technique that he has used for many years for the surgical correction of concomitant strabismus. He always performs the operation in two stages. For convergent strabismus he does a resection of the lateral rectus, first, and six to seven days later the medial rectus is set back with safety sutures. The function of the muscles and the ability to converge are tested on the operating table and the sutures adjusted. He apparently uses local anesthesia and does not operate on young children. Orthoptic exercises are given from the second postoperative day.

An extremely interesting subject—postoperative squint, its correction and prophylaxis—is discussed by Lukić,[76] but only the author's summary was available; consequently, we are left without many of the possibly most interesting details. The author recognizes three groups of postoperative squint: (1) mechanical factors created during the operation by unsatisfactory technique; (2) absence of binocular vision, with or without amblyopia, and (3) growth of the orbits in puberty, causing divergent squint of a paralytic type. The summary, unfortunately, does not give his methods of handling these conditions. As prophylactic measures he advises three types: (1) preoperative (etiological treatment, correction of vision, and orthoptic treatment); (2) operative (good operative technique; free tenotomy should be avoided in favor of a recession), and (3) postoperative (correction of refraction and orthoptic training).

Vila-Coro [77] discusses the surgery of the obliques. He gives detailed descriptions of the various techniques most commonly used for these muscles. This review is a thorough one, but nothing new is added.

The nystagmus which accompanied strabismus was considerably reduced in 13 cases treated surgically by Rama.[78] In 9 cases the nystagmus was purely ocular, the result of insufficient power of fixation. The improvement was both functional and cosmetic.

The muscle and tendon removed at 13 advancement operations were examined by Rama.[79] Generally there were no prominent macroscopic or histologic changes. In some cases, however, there were marked histologic changes, consisting of hypoplasia of muscle fibers and hyperplasia of connective tissue. In these cases he attributes the squint to an anomalous development of the mesodermal tissue.

Defective Abduction.—Four types of defective abduction are discussed by Spaeth.[80] He describes the classic retraction syndrome. He pictures a fan of adhesions from the lateral wall of the orbit to the globe, near the insertion of the lateral rectus, limiting the amplitude of the action of this muscle, and partially fixing the eyeball. The center of rotation of the globe and its position within the orbit have been displaced laterally. Surgery can only correct the manifest deviation, minimize faulty facing and head tilt, and perhaps reduce the deformity from retraction. Tendon transplantation is wholly out of the question. Recession of the medial rectus is the first choice. Exploration of the lateral rectus, resecting pathological bands and releasing hypertrophied check ligaments, and possibly resection of the lateral rectus are second. Surgery of the obliques is rarely indicated and is usually dis-

appointing. Spaeth considers strabismus fixus as a variant of the retraction syndrome, and to be due to a rigid, fibrosed medial rectus that is attached by a very broad insertion to the sclera. Free recession of the medial rectus "in an amount sufficient to obtain maximum results" is indicated. He stresses the difficulty of the operation and the danger of rupturing the sclera.

Spaeth believes that sixth nerve paralysis is probably the commonest congenital paralysis. He advocates operating as soon as the diagnosis is made, preferably before the second year, unless the eyes are straight in the primary position. Care should be taken not to substitute an adduction weakness for an abduction defect. He prefers recession of one or both medial recti, then resection of the lateral rectus or transplantation. For acquired sixth nerve paralysis, after a postponement of 12 months, use of the tendon transplant, within rigid limits, is ideal. If the eye moves spontaneously to the midline on binocular movement, immediate transplantation, with resection of the paretic muscle, is indicated. Recession of the medial rectus may be necessary as a second stage. If the eye does not move spontaneously to the midline, recession of the medial rectus should be the first operation. Then if the eye moves to the midline, the transplantation can be done. Transplantation reduces adduction by reducing the adduction power of the superior and inferior recti. This, plus the resection of the lateral rectus, holds the eye in the midline for the maximum abduction function of the obliques. Transplanted tendons cannot act as abductors; they function only as cicatricial adhesions. It is not uncommon to get abduction recovery of 20 to 30 degrees from the midline. These rules for the use of tendon transplantation and the explanation of how it works, by the foremost exponent in this country, are of great interest.

SUMMARY

There have been a few pessimistic reports on the results of strabismus therapy (Riise, Ruedemann), and a strongly reactionary one that opposes all the modern trends (Parfonry and Polliot). While no one claims to know all the answers, most of the authors show an enlightened and constructive approach to the problem. The great majority start some sort of treatment as early as possible and use occlusion routinely (Bangerter is the one notable exception). It is my impression that more ophthalmologists are employing orthoptic exercises regularly, for appropriate cases, and the limitations of orthoptics are better understood. I find less unanimity about the age of operation. There are still many surgeons, particularly in Europe, who are afraid of early operation, and some who still advise waiting until puberty. Very little that is new in the way of technique of operation has appeared. The resection and recession are the most popular operations, although several surgeons are not willing to do both on the same eye at one operation. The danger of doing too much surgery on one eye is appreciated, and the trend toward dividing the surgical procedures symmetrically between the two eyes is indicated. Specific indications for surgery are given by Lyle and by Rodriguez Barrios and Martinez, while Spaeth has given definite rules for the use of tendon transplantation.

CONCLUSION

In conclusion, it seems to me that the most significant publications to appear during 1953 were the strabismus symposium given at the American Academy of Ophthalmology and Otolaryngology, Rønne and Rindziunski's work on anomalous

correspondence, Bangerter's monograph on the treatment of amblyopia, Knapp's exposition of intermittent exotropia, and, in a distinctly adverse way, the monograph of the treatment of strabismus by Parfonry and Polliot. Adler's evidence for a divergence mechanism may prove to have great significance, and Costenbader's plea for symmetrical surgery possibly marks the beginning of an important trend. There has been a gratifying increase in the number of articles on the treatment of strabismus, from many parts of the world, that show a thorough understanding of the modern principles that are generally accepted in this country.

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Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Truman L. Boyes, M.D., *Chairman*

Charles A. Perera, M.D., *Secretary*

Regular Meeting, Feb. 15, 1954

Fracture of Zygoma and Orbit. Dr. William Rubin (by invitation).

Recent fracture of the zygoma involving the inferior orbital margin should be suspected when there is much periorbital edema. Careful finger palpation and x-ray studies will confirm this suspicion. Later, vertical muscle imbalance, with diplopia, enophthalmos, and ptosis of the globe, makes the diagnosis obvious.

Early fractures are treated successfully by intraoral exposure of the fracture, followed by reduction with controlled leverage, and by wiring according to the method described by the author. This method will be published in detail in a later paper.

Diamox (a Carbonic Anhydrase Inhibitor)—A New Approach to Glaucoma Therapy. Dr. Goodwin M. Breinin (by invitation).

This paper will be published in full in a coming issue of the A. M .A. Archives.

Psychosomatic Aspects of Ophthalmology. Dr. Virginia Lubkin (by invitation).

The author made a plea for increased awareness of psychogenic ocular patterns in daily practice, citing in detail five cases from her office experience. The first was one of puzzling amblyopia in a young girl; the second was a curious case of clonic leg spasm on use of the eyes for reading; the third, a demonstration of the hazards of emotional maladjustment in a case of strabismus; the fourth, a depiction of ocular symptoms of acute anxiety states, chiefly entopic in nature; the fifth, a mistaken diagnosis of oculogyric crises, shown on psychoanalysis to be hysterocompulsive.

A discussion of the psychogenic aspects of headache brought in the researches of Harold Wolff and others into the migraine problem, demonstrating a significant personality pattern.

In a consideration of the reading problems of children, Dr. Lubkin made the point that while there are multiple causative factors, there is no doubt that one of the most important is psychogenic. Subjects have been shown to improve in reading ability after psychotherapy alone, without remedial measures.

The nature of psychogenesis was discussed. The importance of the eye in mythology and folkways through the centuries lends weight to its significance as an unconscious symbol in neurotic disturbances. Evidence from the psychoanalytic literature explores, among other manifestations, varieties of scoptophilic guilt— the guilt of overerotization of the function of vision.

Finally, the important new advances in the experimental study of psychosomatic disease were outlined.

Ocular Neurofibromatosis. Dr. Don Marshall (by invitation).

The general and ocular manifestations of von Recklinghausen's neurofibromatosis were reviewed, and, in more detail, a summary of reported cases of glioma of the optic nerve was presented. About 660 instances of primary optic nerve tumor,

involving the nerve or the chiasm, have been reported. In 108 of these cases Recklinghausen's disease was known to have been associated. Reports in the last 20 years show that this relationship existed in 37.6% of cases of glioma of the optic nerve or chiasm.

One case of optic nerve glioma with familial neurofibromatosis was presented, and two others with neurofibromatosis affecting the eyes.

This paper was published in part in the *American Journal of Ophthalmology* (37:15-36 [Jan.] 1954).

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

George F. J. Kelly, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Oct. 22, 1953

Traumatic Arteriovenous Aneurysms with Bilateral Sixth Nerve Paralysis. DR. JOSEPH C. YASKIN and DR. EDMUND B. SPAETH.

Bilateral abducens paralysis immediately following cranial trauma is not uncommon. It is usually ascribed to the tearing or severe stretching of the sixth nerve in or about the region of Dorello's canal. The occurrence of unilateral sixth nerve paralysis in the course of traumatic arteriovenous aneurysm is, likewise, not uncommon and usually occurs days or weeks after the trauma, coincident with the development of the aneurysm. Bilateral sixth nerve paralysis in the course of arteriovenous aneurysms is rare. It usually develops days or weeks after the trauma and at times presents a problem from the standpoint both of diagnosis and of treatment. We therefore deem it advisable to put on record the following case.

REPORT OF CASE

L. E. (Graduate Hospital #21734), a 65-year-old retired school teacher, with an entirely negative family and past medical history, was involved in an automobile accident on Nov. 18, 1952. She was unconscious for an undetermined period of time. She had an injury to the left knee and rib fractures. Immediately after the accident she perceived a buzzing sensation in her head. This persisted, and three weeks after the accident, while still in the hospital, she noticed difficulty with vision. On Dec. 18 persistent double vision developed. When first seen, on Feb. 23, 1953, she had double vision and tinnitus in both sides of the head, more pronounced on the right. She had no impairment of hearing. The somatic examination was negative except for a blood pressure of 160/90.

The neurological symptoms may be summarized as follows: There was diminution of associated movements of the left arm. Proptosis was present bilaterally, being more marked on the right. There was intense conjunctival congestion. There was bilateral sixth nerve paralysis, more nearly complete on the right. A bruit was audible over the entire skull and over the cheeks; it was loudest over the right eyeball.

When the right carotid artery was compressed, the bruit disappeared, and the patient volunteered that she was no longer able to hear buzzing in the head. Neither the bruit nor the buzzing disappeared on compression of the left carotid artery.

Routine laboratory studies, including an x-ray of the skull, were negative.

On Feb. 25, 1953, a right carotid arteriogram demonstrated a communication between the right carotid artery and the right cavernous sinus. The cavernous sinus was noted to fill bilaterally, and the ophthalmic veins also filled bilaterally. This, however, was felt clinically to result entirely from the injection of the right carotid artery.

Because of the findings, ligation of the right common carotid artery was performed on March 3, with the use of local anesthesia. The patient tolerated the

procedure very well and made an uneventful recovery. The congestion of the left eye completely disappeared and the eye became normal, whereas the right eye seemed to improve for a time but the congestion then became more marked.

On March 12 the right internal carotid artery was ligated. Following this procedure there was complete disappearance of the bruit. After returning to her room, however, she noticed a faint swishing sound in the right side of the head, but it was definitely decreased as compared with the preoperative state. She made an uneventful recovery and was discharged on March 16.

She was examined on April 15, and most recently on June 8, 1953. She had no complaints except for a slight sound in the back of the right side of the head. There was no bruit in any part of the head and only a slight change in pitch over the right carotid artery. Only slight proptosis of the right eyeball was evident. There was no extraocular paralysis and no other neurological abnormality.

Comment.—It is reasonable to assume that the bilateral sixth nerve paralysis was due to the compression of the sixth nerves by the dilated cavernous sinuses. Prior to the operative procedures, there was some doubt whether this was the only mechanism that would explain the bilateral abducens paralysis. The therapeutic end-results in this 65-year-old patient were very gratifying, and that in itself justifies publication of the case.

DISCUSSION

Dr. Edmund B. Spaeth: There are three comments to be made from an ophthalmological standpoint. Eight years ago Dr. Krewson and I had occasion to write a rather exhaustive paper on intracranial aneurysms and intracranial arteriovenous fistulae. We found that 64% of all intracranial aneurysms, including arteriovenous fistulae, had oculomotor manifestations. In these cases third nerve involvements were outstanding. Sixth nerve involvement was present in only about 20% of cases. In the majority of these cases there were arteriovenous fistulae. Both sixth nerves were involved in only a very small number.

Dr. Yaskin's statement is certainly beyond question: "Following the release of pressure inside the cavernous sinus there followed complete recovery from the sixth nerve paralyses." Considering the anatomy of the cavernous sinus and the sixth nerve, it is rather difficult to understand why both sixth nerves were involved. Certainly, the impact of the arteriovenous aneurysm on one side should not affect the opposite sixth nerve. There was no cavernous sinus thrombosis, though there probably was an increased intersinus pressure, as indicated by the venous engorgement of the retina.

One other point is to be mentioned here. Weinstein, of Budapest, recently called attention to a syndrome of cavernous sinus pressure. In this syndrome digital pressure upon the jugular vein will not stop spontaneous venous pulsation in the retina if increased pressure is present within the cavernous sinus. This syndrome was not present in the case under discussion.

Dr. George F. J. Kelly: A number of years ago I had under my observation a patient with pulsating exophthalmos, traumatic in origin. Dr. George M. Dorrance ligated the common carotid and then the internal carotid artery on one side. The patient did not improve, and the condition became bilateral, with ensuing optic atrophy.

I should like to ask Dr. Yaskin whether, in his experience in cases of this type, he is able to forcast the possibility of optic atrophy or hemiplegia developing after carotid ligation?

Dr. Joseph C. Yaskin: I shall attempt to answer the two questions propounded by the discussants. The ligation of the common and internal carotid arteries is in most instances a fairly safe procedure. The permanent ligation is usually preceded by digital compression or application of a clamp, or even a ligature, for minutes or hours to determine whether or not the collateral circulation is sufficient to take care of the deprivation of blood supply from one side. Transient mild hemiparesis often

follows permanent ligation. I have never seen any blindness from ligation of the carotid vessels. Most of the patients whose arteries were ligated had relatively healthy blood vessels except for the presence of an aneurysm.

The surgical management of intracranial aneurysm has undergone a great change in the last 15 years. The diagnosis is more frequently suspected by reason both of subarachnoid bleeding and of the involvement of the third nerve. The involvement of the sixth nerve rarely occurs in intracranial aneurysm but, of course, is much commoner in arteriovenous aneurysms, which are usually traumatic in origin. The surgical management of these cases depends entirely upon the location and type of the aneurysm. A saccular aneurysm with a neck can be ligated in almost any location. Aneurysms arising from the anterior cerebral and middle cerebral arteries are not favorable for direct attack. In these aneurysms the ligation of the internal carotid is sometimes helpful. Fortunately, the anomalies of the circle of Willis are so common that unexpected anastomoses take care of a great many difficult situations. Thus, in one of our patients Dr. Groff found an aneurysm involving the Sylvian artery. He tried to protect it by supplying muscle tissue around it, but it ruptured while the patient was on the operating table. He was compelled to ligate the middle cerebral artery. Surprisingly, the patient did extremely well and, indeed, has made a gratifying recovery.

Some Aspects of Torsion. Dr. J. V. D. Quereau, Reading, Pa.

This paper was published in the June, 1954, issue of the Archives, page 783.

DISCUSSION

Dr. Francis H. Adler, Reading, Pa.: Dr. Quereau has very clearly defined what false torsion is and how it compares with what we call true torsion. One might say that Dr. Quereau has laid the ghost of true torsion in the oblique positions of gaze, and that it would take somebody with considerable temerity to try to disinter it. There are, however, a number of questions which remain to be answered, and I am sure that Dr. Quereau will agree that many of the problems connected with torsion have not yet been solved from a practical point of view.

It makes no difference whether we call the position of the vertical axes true torsion or false torsion, the fact remains that in the oblique positions of gaze the vertical meridians of each eye are tilted in respect to the horizontal and vertical lines of space. If one uses spherical ordinates, then, as Dr. Quereau has shown, there is no tilt. From a practical point of view, we really are not concerned whether there is true or false torsion in the oblique positions of gaze so long as the vertical meridians of the two eyes remain parallel. What is of importance is to know the muscles which are activated in turning the eyes into the oblique positions of gaze. It has been pointed out that when the eyes move in the horizontal position, five of the six muscles in each eye are cocontracting. When an eye moves vertically, four of the six muscles are cocontracting, and when an eye moves obliquely, three of the six muscles are cocontracting. The other muscles are undergoing inhibition, known as reciprocal innervation. If one analyzes the muscles which are employed in the oblique positions of gaze, it becomes evident that there will always be an imbalance between the muscles that produce intorsion and those that produce extorsion, and this imbalance always turns out to be that which we find when we measure "false torsion." For example, when the eyes are looking up and to the right, the muscles in the right eye which are contracting are the right lateral rectus, the right superior rectus, and the right inferior oblique. As the eye moves from the primary position up and to the right, the right superior rectus becomes entirely an elevator and produces no intorsion. On the other hand, the right inferior oblique loses its elevating activity and produces more and more extorsion. The end-position, when the right eye is looking up and to the right, is extorsion. I should point out that the eyes are not moving around any fixed axes that have anatomical existence, but that the muscles which move the eyes do so in a manner as though the eyes were moving about fixed axes. What we really need to know is the activity of

each of the ocular muscles in all positions of gaze. We demonstrated that when the eyes are looking straight up, the lateral and medial rectus muscles are cocontracting. No one as yet has shown what muscles are actively cocontracting in oblique positions of gaze, but I hope that when this has been done experimentally, the results will not conflict with what Dr. Quereau finds from his observations.

This paper has clarified the confusion which exists in the literature between false and true torsion, and from this point of view alone it is a valuable contribution.

DR. WILLIAM E. KREWSON III: I should like to ask Dr. Quereau if he has any idea of the torsion that occurs in convergence.

DR. J. V. D. QUEREAU, Reading, Pa.: In reply to Dr. Adler, I am not sure that real torsion does not occur in these oblique directions, but I have not been able to see it. I am sure that I find real intorsion in the downward and outward oblique direction. The reason this has not produced diplopia in the patients I have observed is that in this extreme rotation the nose is in the way of the other eye. If thousands of observations could be made, perhaps some pattern would emerge; then we should know whether torsion does occur normally in the oblique cardinal directions. I hope this method of observation will prove practical, so that those observations can be made.

In answer to Dr. Krewson's question, I believe one could not test for the torsion of convergence by this method. This method will test only for torsion in the oblique direction into the field of action of a muscle. We are now trying to devise an artificial Listing plane with an arc in the front, situated above the center, which is coincident with the center of rotation, and on that we hope to rotate a hairline. The only trouble with using a line for reference is that the line itself gets in the way; it becomes cumbersome and the observation useless. I have not been able to test for any of the torsional effects of convergence.

Relationship Between Coreal and Total Astigmatism. DR. EDWIN FORBES TAIT.

A survey was made of 2,068 eyes selected at random from a larger number reported on, examination of each including careful determinations of corneal astigmatism with the ophthalmometer and the lens correction for refractive error, the latter being verified for accuracy at a later date or by successive refractions.

The distribution of the anterior corneal curvature for 2,000 of the eyes for the primary meridian, secondary meridian, and mean values is reported in millimeters of radius and in diopters, the latter based upon a refractive index of 1.3375. Comparison with the data of previous investigators shows a general agreement. The range of mean values, except for a very few eyes, was between 7.2 and 8.4 mm. of radius (40.00 and 47.00 D.), with the high point of the curve about 7.8 mm. (42.00 D.).

The degrees of astigmatism ranged from practically spherical corneas, in a few eyes, to 5.00 D., the majority of eyes presenting 0.25 to 1.25 D. of astigmatism, with the mode around 0.75 D. Of these 2,000 eyes, the astigmatism of 1,872, or 93.6%, was with the rule, and that of 122, or 6.1%, was against the rule. None of the 122 eyes with astigmatism against the rule exceeded 1.50 D.

Each astigmatic value obtained by the ophthalmometer was equated to a cylindrical lens value when the latter was situated at 12 mm. in front of the cornea. Inasmuch as the effectivity of the cylindrical lenses in that position is controlled by the spherical elements associated with them in the lens correction, the refractive condition in each individual eye was calculated and the cylindrical lens determined that at 12 mm. would just neutralize the corneal astigmatism.

The difference between this effective cylinder lens and the astigmatic element in the final lens prescription is equal to the intraocular astigmatism.

Four age groups—5 to 10, 15 to 25, 30 to 45, and 50 to 65 years—were studied, with 400 eyes in each group. In each group the majority of eyes exhibited between 0.25 and 0.75 D. of intraocular astigmatism against the rule, with the high point

of the distribution curve in each case at 0.50 D. There was, however, a gradual increase in the over-all distribution in each successive age group, with a relatively larger number presenting 1.00 to 1.25 D.

A very few cases had with-the-rule intraocular astigmatism, mostly of the order of 0.25 D., with several scattered eyes presenting somewhat higher values.

During the process of random selection of 2,000 eyes with regular corneal astigmatism, 68 eyes with irregular curvatures were found. These all presented an appreciable reduction in visual acuity with lens correction as compared with the larger group. Slit-lamp studies made at the time of the original examination revealed no apparent tissue abnormalities or perceptible variations in curvature. The ophthalmometer test, however, demonstrated the presence of minimal, but typical, keratoconus distortion in 12 eyes and meridional irregularities in 56 eyes. Without the help of the instrument, the reason for the lowered visual acuity could only be surmised.

Summary.—The author believes the investigation shows that the ophthalmometer can be of help (1) in an analytical refractive process in making possible the diagnosis of the lenticular compensatory astigmatism which occasionally accompanies a ciliary muscle hypertonus; (2) in the refraction of children; (3) in the detection of anterior corneal irregularities which interfere with vision; (4) in cases of anisometropia, in order to determine whether the refractive difference in the eyes is on a basis of anteroposterior globar length or of corneal curvature, an important aid in diagnosis of aniseikonia, and (5) in the routine refractive procedure as an additional source of very reliable information as to the power of the major refracting surface of the eye. A knowledge of the usual limits in the distribution of intraocular astigmatism in various age groups will act as a warning when ophthalmometer findings are available and the usual limits are exceeded, and thus eliminate possible gross errors in correction of refractive errors.

DISCUSSION

DR. ALFRED COWAN: It is a pity that the ophthalmometer has fallen into such disuse that most men do not employ it at all. I think every ophthalmologist should at least know how to use it. Dr. Tait brought out many points, some of which are pretty well known. First of all, the ophthalmometer is not an instrument to be depended on for determination of the total astigmatism of an eye. But the ophthalmometer is a very useful instrument. With it you can determine the difference of ⅛ D., and that means that you are measuring differences in radii of curvature of about 0.025 mm. It is to a certain extent a useful instrument clinically provided that your findings are properly noted.

The ophthalmometer is of hardly any use at all, as Dr. Tait implied, if you merely note that with it you find an astigmatism of 1 D. with the rule, or 1 D. against the rule, or the like. If the findings are properly noted, you have some information that may be useful. For example, if with the ophthalmometer you find that the dioptric power of a cornea is, say, 46 D. in the vertical meridian and 45 D. in the horizontal meridian, make the notation that way. Then you know that there is 1 D. of astigmatism with the rule, and that the curvature of the cornea corresponds to what is considered the ophthalmometric standard, which is about 45 D. Also, the moment you look at an eye with the ophthalmometer, any irregular astigmatism or irregularity in the surface of the cornea will be seen immediately. Dr. Tait verified the fact that the intraocular astigmatism—the astigmatism produced by the posterior surface of the cornea, the anterior surface of the lens, the posterior surface of the lens, and the tilting of the lens—seldom amounts to more than 1 D. That, as Dr. Tait says, is the whole amount of the intraocular astigmatism. Usually it is against the rule. The curvature of the cornea changes very slightly throughout life, so that the change in the astigmatism of an eye in the course of years is due chiefly to the changes in the intraocular astigmatism, which, as I said, is mostly against the rule. But when we say that the astigmatism is against the rule, we do

not mean that the axis is exactly 90 or exactly 180 degrees. We do not mean that because we say that the astigmatism of the cornea is with the rule, and that the astigmatism of the so-called residual, the intraocular, astigmatism is against the rule, the axes are necessarily at right angles to each other. Usually the axes of the two components are obliquely crossed. Therefore the axis of the astigmatism of the resultant combination, the total astigmatism, is neither the axis that we find with the ophthalmometer nor the axis of the astigmatism inside the eye. The axis of the total astigmatism must lie between the two oblique axes. Consequently, from the standpoint of an instrument for the determination of the total astigmatism of the eye, the ophthalmometer is not of very much use except in aphakia or in cases in which the astigmatism of the cornea is so predominant that the total astigmatism must correspond to it merely because of the greater amount of corneal astigmatism than of intraocular astigmatism. In that way, we may find it of some use in refraction. But generally, as Dr. Tait stated, it cannot be depended on as an instrument to help much in determination of the refraction.

Edmund B. Spaeth, M.D., *Chairman*

William E. Krewson III, M.D., *Clerk*

Feb. 18, 1954

Ophthalmoplegias of Neural Origin. Dr. C. Wilbur Rucker.

Experience with opthalmoplegias of neural origin was summarized, and several illustrative cases were presented. Analysis of 282 cases disclosed that in about 25% (67 cases) the cause was not determined. Head injury accounted for another large group (52); of these, an automobile accident was responsible for over one-half.

Aneurysm at the circle of Willis was the cause in 31 cases, and in two-thirds of these the oculomotor was the nerve implicated. In every case of third nerve paresis due to aneurysm there was some iridoplegia.

Occlusive vascular disease seemed to account for many (54) of the pareses. In this group the patients presented evidence of hypertension or arteriosclerosis, and a few had diabetes. In the majority of these the pupillary reactions were intact, and there was a tendency to recovery.

When brain tumor was responsible for ocular paralysis, the abducens was by far the most frequently affected, and sixth nerve paresis was of no localizing value. The third and fourth nerves were involved by tumor uncommonly.

Syphilis was responsible for five cases of abducens paralysis and one case of paresis of the third and sixth nerves. Its incidence is much lower than it was in former years.

Multiple sclerosis accounted for 11 cases of sixth nerve paresis. In no case did it affect the third or fourth nerve.

The group of miscellaneous rare cases was not discussed.

Obituaries

LE GRAND HAVEN HARDY, M.D.
1894-1954

Dr. LeGrand Haven Hardy died of a heart attack on April 14 in the Harkness Pavilion of the Presbyterian Hospital in New York, at the age of 59.

Dr. Hardy was born in Provo, Utah, June 15, 1894, the son of Milton Henry Hardy and Elizabeth Smoot Hardy. His father, one of the pioneer educators in Utah, was a well-known psychiatrist. The town of Dr. Hardy's birth lies at the foot of high mountains, and during his early manhood LeGrand became an enthusiastic mountain climber. He was among the first to climb some of the high peaks in that vicinity.

His college education started at Brigham Young University, where he obtained his A.B. degree in 1916. Before he entered medical school, he studied engineering and, after pursuing work at the University of Chicago in 1916, received a B.S. degree from Columbia University in 1919. His knowledge of mechanics and his facility in mathematics largely influenced his later life and conditioned his interest in physiologic optics, in which he was to become prominent. Having determined on a medical career, he entered the College of Physicians and Surgeons and received his M.D. degree in 1921. He must have had considerable interest in psychiatry at this time, probably due to his father's success in this field, for prior to embarking on his training in ophthalmology he served a psychiatric internship.

He began the practice of ophthalmology in 1922 and served as an Assistant Surgeon at the New York Eye and Ear Infirmary from 1922 to 1924. He became ophthalmologist to the Northern Dispensary in 1924 and served until 1929, when he became a Consultant there, a position he held until his death. From 1925 to 1936 he was Ophthalmic Surgeon at the Midtown Hospital, and from 1929 to 1936 he was Director of Ophthalmology at the Fifth Avenue Hospital. In 1936 he was named Professor of Clinical Ophthalmology at the Columbia University College of Physicians and Surgeons, and Attending Ophthalmologist at the Presbyterian Hospital and Vanderbilt Clinic. At the time of his death he was also Director of the Knapp Memorial Laboratory of Physiologic Optics in the Institute of Ophthalmology, Presbyterian Hospital.

He was a Fellow of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the American College of Surgeons, the American Medical Association, the New York Ophthalmological Society, the American Association for the Advancement of Science, the Association for Research in Ophthalmology, and numerous other scientific and cultural groups, such as the International Color Council. He was one of the pioneers in the founding of the American Orthoptic Council, and was its first president.

His interest in and knowledge of physics and mathematics soon turned his energies into the field of optics and illumination, and most of his writings which continue to be authoritative sources of information are on these subjects. His most recent publications include the final reports on his researches for the Office of Naval

Research entitled, "The Geometry of Binocular Space Perception," and a new test for the "Detection, Classification, and Estimation of the Degree of Defective Color Vision."

Dr. Hardy had an inquiring and imaginative mind and read widely not only in many different fields of science but also in philosophy, philology, and exploration. He had an infectious enthusiasm, which kindled the interest of those who had the opportunity to listen to him expound on such subjects. Even if the listener was occasionally unable to follow the thread of argument as it poured too fluently from his facile mind, he carried away the zeal and spirit with which it was delivered.

As an avocation, he loved to work with his hands and was an expert mechanic and carpenter. He had his own shop in his lovely country place in Bucks County,

LE GRAND HAVEN HARDY, M.D.
1894-1954

Pennsylvania, and one at the hospital, where he personally made many of the instruments used in his experiments. The last thing he embarked on last summer was the reconstruction of a jeep to use on his farm. He was also an eager fisherman and woodsman.

Conversation with a few intimate friends was one of his chief joys in life, and on such occasions the faint sparkle of wit from his half-closed eyes could grow to fiery and eloquent pronouncements. Although dynamic, he was always gentle and kindly, and he endeared himself to all those who knew him. Ophthalmology has lost not only a leader in the investigative field, but a much-beloved personality.

He is survived by his widow, the former Miss Susanna Haigh, whom he married in 1923.

FRANCIS HEED ADLER, M.D.

News and Comment

GENERAL NEWS

Hardy Memorial Research Fund.—In recognition of the great interest of LeGrand H. Hardy in the study of physiological optics, a fund is being established for furthering research in this subject, to be known as the Hardy Memorial Research Fund. Contributions may be sent to The Hardy Memorial Research Fund, Institute of Ophthalmology, 635 W. 165th St., New York 32.

PERSONAL NEWS

Appointment of Dr. Fred M. Wilson.—The appointment of Dr. Fred M. Wilson as chairman of the Department of Ophthalmology in the Indiana University School of Medicine was announced today by Dean John D. Van Nuys.

The appointment of Dr. Wilson was made by the University trustees upon recommendation of Dr. Robert J. Masters, who is relinquishing the chairmanship he has held for the past eleven years, to devote full time to his private practice. Active in the expansion of the eye clinic and teaching program for many years, Dr. Masters will continue on the staff as professor of ophthalmology.

Dr. Wilson, who holds the A.B. and M.D. degrees from Indiana University, served as resident in ophthalmology at the Indiana University Medical Center after military service in World War II. He did graduate work in his specialty at Bellevue Medical Center in New York and was a faculty member in ophthalmology at the University of Illinois College of Medicine, in Chicago. He had practiced in Austin, Texas, before joining the staff of the School of Medicine here three years ago.

Married and the father of three children, Dr. Wilson resides at 7615 Westfield Blvd. He is a member of several medical and ophthalmological societies and was recently elected chairman of the Indiana Committee of the National Society for the Prevention of Blindness.

SOCIETY NEWS

New York Society for Clinical Ophthalmology.—At a recent meeting of the New York Society for Clinical Ophthalmology Dr. Frederick H. Theodore was elected president for the 1954-1955 session and Dr. Jesse M. Levitt was elected recording secretary. Dr. L. H. Ehrlich will continue to serve as corresponding secretary.

INDEXES

This issue of the ARCHIVES appears in two parts, the second of which is the index for the preceding volume. To make the index more usable to the readers and to enable them to find information with less difficulty than has been encountered in previous volumes, the index has been broken down into three separate indexes: Title Index, Author Index, and Subject Index. The Title Index, which will take the place of the six-month Table of Contents, previously published with the index of the journals, has been prepared in such form that it can be separated from the other indexes and bound in the front of the volume. It consists of the titles of the articles arranged in alphabetical order and accompanied by the name of the author, the name of the senior author if there are more than two, the names of both authors if there are two, and the page number on which the article begins. The Author Index contains the names of all authors of articles appearing in the ARCHIVES and of the presenters of cases or papers before societies. The third index, the Subject Index, contains in alphabetical order the important subjects which have been dealt with in the volume. Individual abstracts are no longer indexed; only the categories under which they have been classified are listed. Book notices and news items are included in this Index.

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Plano Meniscus
6.50 Base Rough Cylinders and + or − S.F. Meniscus

B Shade—Bifocals

4.00 and 6.00 Base A Ultex, Regular Size
4.00 and 6.00 Base A Twinsights, Regular Size
4.50 and 6.50 Base K Ultex, 80 m/m Rd. and Regular Size
4.50 and 6.50 Base B Ultex, 80 m/m Rd. and Regular Size
4.50 and 6.50 Base Kurova D, Regular Size

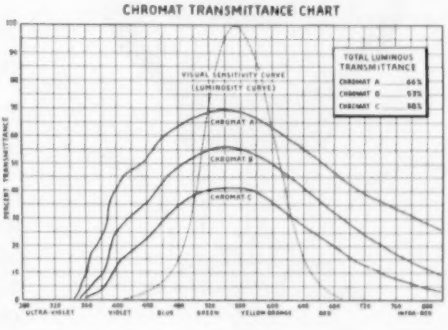
C Shade—Single Vision

Finished Kurovas, 54 x 57 m/m King Size
Plano Meniscus
4.50 Base Rough Cylinders and + S.F. Meniscus
6.50 Base Rough Cylinders and + or − S.F. Meniscus
9.50 Base Rough Cylinders and + S.F. Meniscus

C Shade—Bifocals

6.00 Base A Ultex, Regular Size
6.00 Base A Twinsights, Regular Size
6.50 and 8.50 Base K Ultex, 80 m/m Rd. and Regular Size
6.50 Base B Ultex, Regular Size
6.50 Base Kurova D, Regular Size

CHROMAT TRANSMITTANCE CHART



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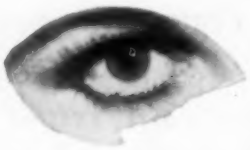

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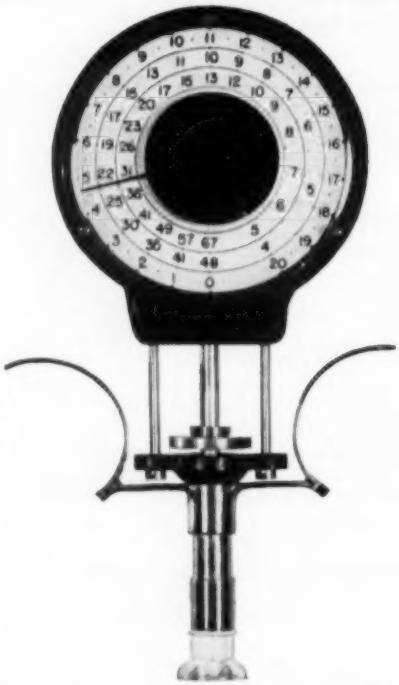

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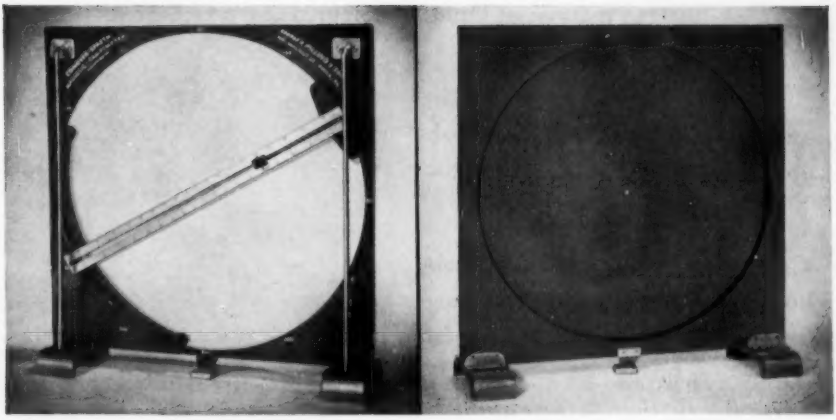

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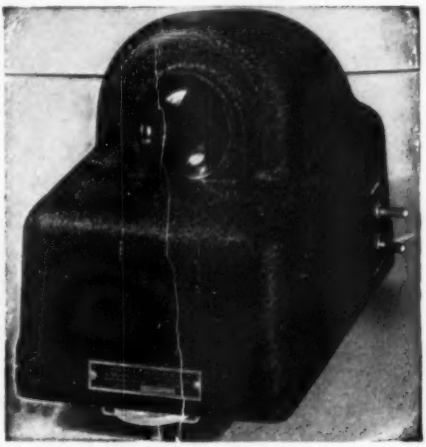

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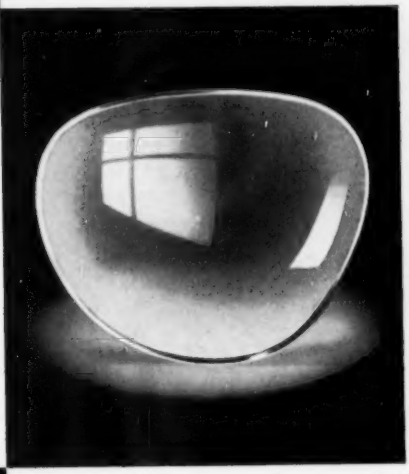

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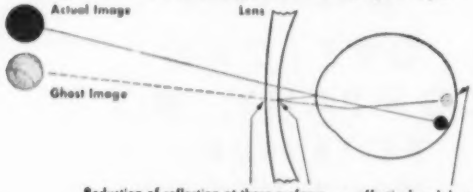

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